VOLUME 53 NUMBER 4 APRIL 1960

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of the

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CONTENTS

Continued overleaf

CONTENTS (*continued*)

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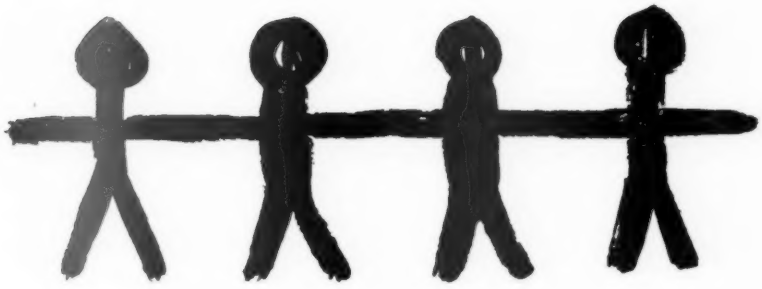

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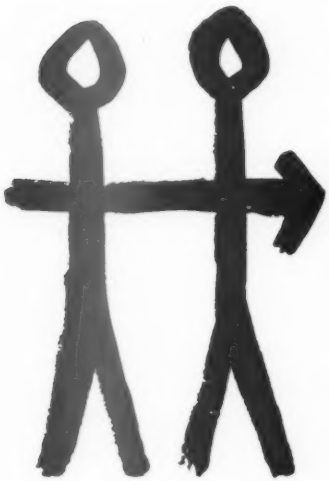

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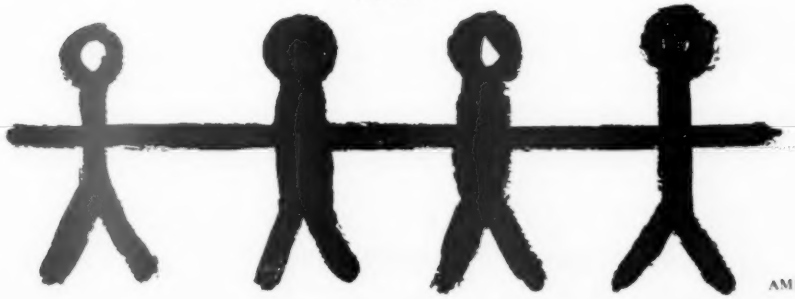

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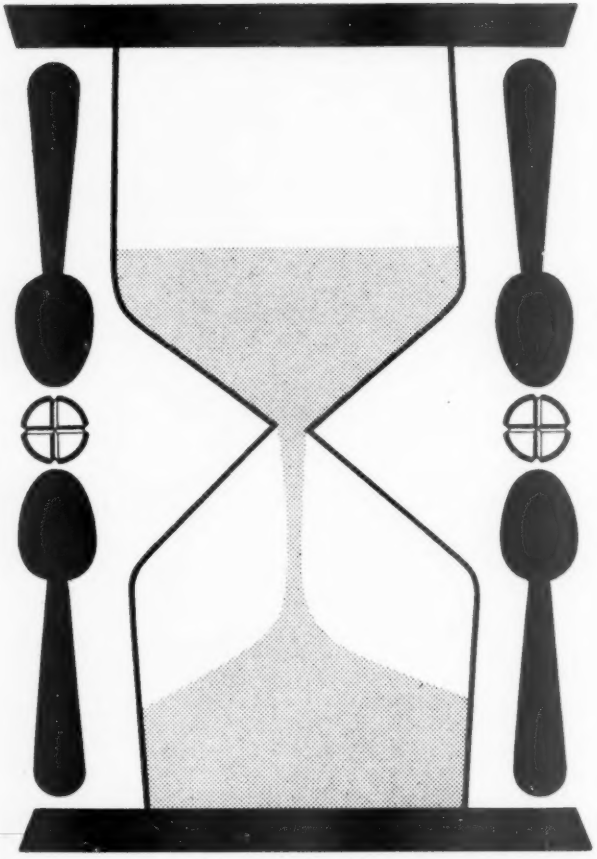

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Meeting
October 16–17, 1959

JOINT MEETING WITH THE FACULTY OF RADIOLOGISTS

SYMPOSIUM ON MYELOMATOSIS

THE following papers were read:

At the Royal Society of Medicine

The Pathology of Myelomatosis.—Dr. B. J. LEONARD.

Serum Protein Changes in Multiple Myelomatosis.—Dr. A. S. MCFARLANE.

The Nature of the Myeloma Globulin.—Dr. JOHN L. FAHEY (Bethesda, Md.).

At the Royal College of Surgeons

Radiological Aspects.—Dr. IRVAN YENTIS.

Radiotherapy.—Dr. J. F. BROMLEY.

Chemotherapy.—Dr. R. C. S. POINTON.

The meeting will be reported in full in *Clinical Radiology, The Journal of the Faculty of Radiologists.*

Meeting
January 15, 1960

SOME CLINICAL ASPECTS OF MEGAVOLTAGE[1]

Seminoma of the Testis

By ROBERT GIBB, M.B., D.M.R.T., F.F.R.
Manchester

THIS series of contributions is concerned with the clinical experience at the Christie Hospital since 1955 with the 4 MV linear accelerator, in the treatment of certain malignant conditions. These are interim reports and in no case are five-year results available for study. In the past three to four years, however, certain treatment methods have evolved. In order to avoid repetition in the other papers some general remarks common to all can be made here.

Clinical work carried out before the results of the Relative Biological Efficiency (R.B.E.) experiments became available, had suggested that a higher dose of radiation at 4 MV levels was necessary to achieve a given effect, as compared with 250–300 kV. This was confirmed by the experimental results, which pointed to the figure of 85 as the R.B.E. for 4 MV radiation, compared to 100 for conventional therapy. To begin with, all megavoltage doses were not stepped up by this factor, and there was an initial period in some cases where tumour doses were lower than those now in use. Straight dosage comparison with previous cases treated by conventional radiation has been complicated for us by the introduction, not only of the rad in place of the röntgen, but also by the corrected depth dose tables for the 250–300 kV machines at the Christie Hospital. A number of random selection clinical trials, contrasting 250 or 500 kV with 4 MV radiation, are in progress at the moment, but the results are not yet ready for reporting. In the papers which follow comparison will be made between treatment methods and short-term results of small field megavoltage therapy in certain sites, with similar cases treated in the past by other radiation methods. Large field therapy will be considered, using seminoma as an example.

In the prophylactic treatment of seminoma following orchidectomy, certain principles have become accepted practice at the Christie Hospital.

(1) The irradiated volume includes the scrotum and the inguinal, iliac, and para-aortic lymph-node areas. Although recurrence locally in the scrotum occurs only rarely, it is considered advisable to treat the affected side. Whilst it

[1]Papers by the Staff of the Christie Hospital, Manchester.

may be desirable to preserve the remaining testis, attempts at shielding it have two drawbacks—the likelihood that the shielding will only be partial, with subsequent genetic risks, and the danger of the shield slipping over to the affected side during treatment, and diminishing the dose delivered there. It is, therefore, our practice to irradiate the whole of the scrotum. In treating the inguinal nodes routinely, it is appreciated that metastases only occur there when the scrotum is involved, and their inclusion in the treated volume is, in part, due to the technique which has been employed.

(2) The volume to be treated should be irradiated in one block, without the need for matching field edges. This avoids the possibility of a low dose due to a gap between the fields, or an unduly high dose due to overlapping of the fields.

(3) The volume should be irradiated as homogeneously as possible.

The story of the evolution of the treatment technique is of some interest. Very briefly it started using 250 kV X-rays, with an opposed pair of 30 cm circular fields, anterior and posterior (Fig. 1). This suffered from the usual limitations of low central dose and high skin dose. An improvement was the 3-field trunk bridge—an angled pair of anterior fields 30 × 22·5 cm opposed by a posterior 30 cm circular field (Fig. 2). This improved the dose distribution, but the main volume was still not very homogeneously irradiated, with the maximum dose about the level of the skin of the abdominal wall. The lower limit of the treated volume was the perineum, and the level of the upper edge varied with the length of the patient. This method was superseded by the familiar four-field trunk bridge (Fig. 3), using 30 × 22·5 cm rectangular fields, which increased the volume homogeneously irradiated. In spite of the large volume treated, patients tolerated this treatment satisfactorily, without undue drop in the white blood count or troublesome radiation sickness. It was therefore decided that the fields should be lengthened to extend from the perineum to the dome of the diaphragm, and that beam flattening filters should be used to improve the depth dose at the top and bottom of the field. This was the method which was found to cause renal damage due to the inclusion of the kidneys in the high dose zone. Kunkler *et al.* (1952) demonstrated that a homogeneous dose of 2,000 rads, or over, in five weeks, to the whole of both kidneys may cause hypertension and renal failure and also showed that in the earlier techniques mentioned above, renal failure did not occur. This was because the upper third of the kidneys had received 1,500 rads or less in five weeks. It was therefore essential to protect the kidneys, and as lead shielding was not practical owing to the angled fields of the bridge, a return was made to the three-field method, omitting beam flattening filters. For additional safety, an

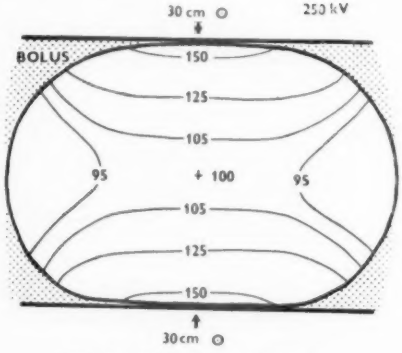

FIG. 1.—Parallel opposing pair.

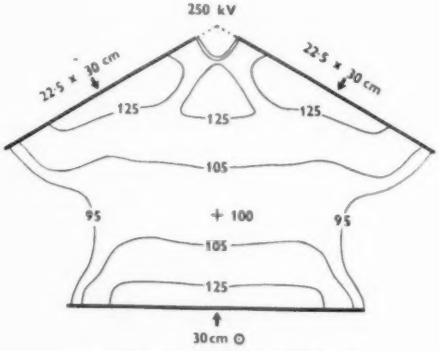

FIG. 2.—Three-field trunk bridge.

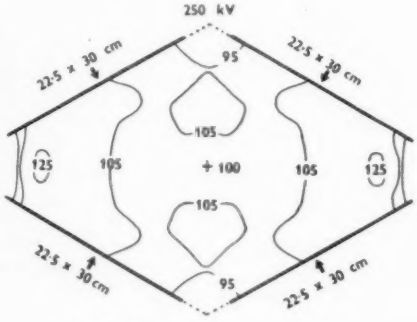

FIG. 3.—Four-field trunk bridge.

intravenous pyelogram (I.V.P.) was done and the fields were so arranged that the upper third of the kidneys received a dose not greater than that shown to be safe. The tumour dose was 2,500 rads, and this was achieved in about five weeks by a daily input which rose from 25 to a maximum of 75 rads per field. The gradually increasing input was considered to lessen the likelihood of radiation sickness and sudden leucopenia. My colleague, H. C. Warrington, decided to try an even daily input of about 125 rads per field, and the overall treatment time was reduced to four weeks, for the same dose, without apparent ill effect to the patient.

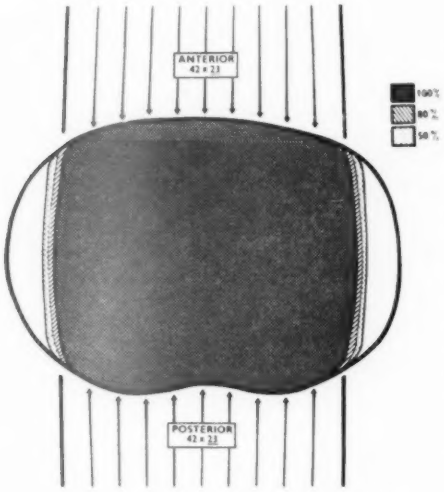

FIG. 4.—Seminoma testis—abdominal bath.

About two years ago the linear accelerator became available for large field therapy, and seminomas were treated by it. Treatment reverted to a parallel opposed pair of fields, but with several important differences from the older techniques. No longer was it confined by applicators to circular or rectangular irradiated volumes. Fields of any desired size became available, and irregular shapes became possible by the interposition of lead blocks in the beam. With 4 MV radiation, depth dose is almost unaffected by the field size, and homogeneous radiation can be achieved in the treated volume, no matter what its shape (Fig. 4). This has the advantage that the kidneys can, if necessary, be completely shielded, whilst the para-aortic nodes lying between them receive adequate radiation.

The present prophylactic treatment of seminoma after orchidectomy is as follows: An I.V.P. is done, with a wire marker placed over a line drawn on the skin of the anterior abdominal wall, about the level of the iliac crests (Fig. 5). A Perspex ruler, on which the centimetre divisions are enlarged to the same magnification as the radiograph, is used for measuring the size

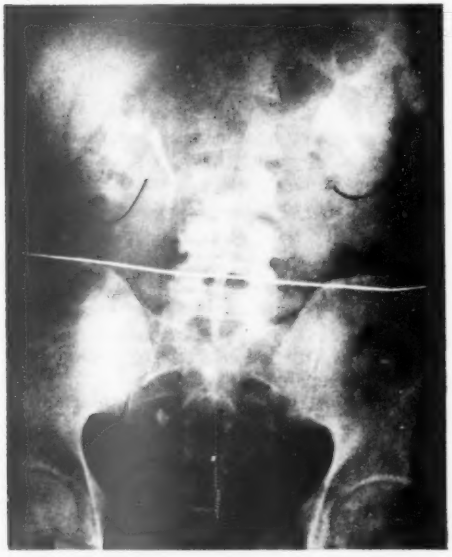

FIG. 5.—Intravenous pyelogram with marker wire.

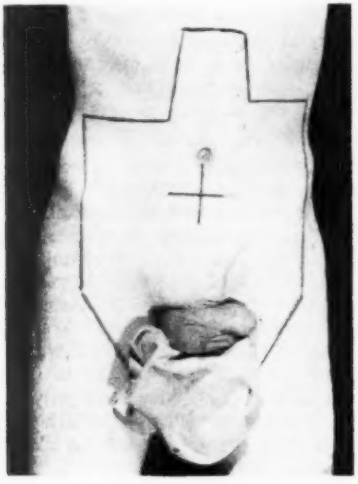

FIG. 6.—Anterior field with scrotum bagged up.

and position of the kidneys in relation to the marker wire. From these measurements the position of the medial edges and lower poles of the kidneys is transferred to the patient's skin, and during treatment the kidney areas are completely shielded. The upper margin of the anterior field is placed at the level of the xiphisternum, allowing generous clearance of the upper para-aortic nodes. The lower edge is at the perineum. In general the scrotum can be pushed upward, thus reducing the field length (Fig. 6). The width treated is less than that with the bridge technique, but includes the iliac nodes and the greater part of the inguinal node area. A careful note is made of the position of the upper edge of the field, in case it is later necessary to irradiate the chest. The post-irradiation skin changes are not sufficiently obvious later to be an adequate guide to the position of the field edges, and recently we have been experimenting with tattooing with indian ink at the important points, to give an indelible mark. A replica of the anterior field is marked on the back of the patient. The usual size of the irradiated area is about 800–900 sq. cm, achieved with an F.S.D. of 130–150 cm. The tumour dose is 3,000 rads in four weeks, treating five days per week, and anterior and posterior fields are treated on alternate days. Bi-weekly blood counts are done, and there appears to be less of a drop in the white cells than with 250 kV. A comparison of twenty patients treated by 250 kV with a similar number at 4 MV, shows, however, an almost identical drop in the count. Radiation sickness and bowel reaction do not appear to differ significantly between the two techniques, but in general the patients treated by 4 MV seem to have an easier time. There is still difficulty in shielding adequately the remaining testis, and this is only attempted when the patient demands it. He is advised that no guarantee can be given as to the completeness of the shielding.

Where metastatic disease is present in the abdomen when the patient is first seen, shielding of the kidneys may not be practicable, particularly when a para-aortic mass overlies one or both. In such cases the whole volume, including the kidneys, is irradiated to 2,000 rads in about three weeks, by which time the metastatic mass has generally resolved enough to allow some shielding of kidney tissue, and with this in position treatment is continued to 3,000 rads in four weeks. If shielding is not possible owing to the presence of disease, the risk of kidney damage is accepted and treatment continued to full dosage.

Patients presenting with lung metastases, but without abdominal metastases, are treated by an opposed pair of fields to the chest, and lungs, mediastinum and supraclavicular fossæ are included in the treated volume, the dose being 2,500 rads in four weeks. Again careful note is made of the position of the lower end of the field, to facilitate abdominal irradiation later, if called for.

For patients with both abdominal and lung metastases when first seen, a technique known as the "moving strip", which irradiated the whole of the trunk, was used many years ago. With conventional radiation the maximum dose to each strip was about 1,400 rads in eight days. Blood tolerance was a problem, results were poor, and the method fell into disuse. It was reintroduced about three years ago, using the accelerator, and it was found possible to give the abdominal strips 2,500 rads, and the lungs 2,250 rads, in eight days, with an overall treatment time of about two and a half to three months.

Of 12 patients with abdominal and lung metastases none survived for a reasonable length of time considering the very prolonged treatment. The one long-term survivor had an orchidectomy for a seminoma and presented with an upper abdominal mass and a large left supraclavicular node, which were accepted clinically as metastases. Both the masses resolved as a sensitive tumour would be expected to, and the patient remains free of disease at two and a half years. The primary was histologically proved, but it now seems a great pity that the supraclavicular node was not also biopsied. Apart from this one patient it appears that palliation can equally well, or even better, be provided by some simpler and less time-consuming treatment, although with seminoma it is probably always right to be hopeful of permanent regression, even with advanced disease. For the present, the moving strip has again been discarded.

To sum up, 4 MV radiation has simplified the technique of treating the abdomen and the chest in seminoma. Not only has it enabled a homogeneous dose to be given throughout the treated volume, but the use of irregularly shaped fields has been possible without loss of homogeneity. It also appears that the patient tolerates the treatment of large volumes by megavoltage radiation rather better than by the methods previously available.

REFERENCE

KUNKLER, P. B., FARR, R. F., and LUXTON, R. W. (1952) *Brit. J. Radiol.*, **25**, 190.

A Wedge Filter Approach With 4 MV Radiation to the Treatment of Carcinomata of the Alveolus and Antrum

By J. G. Stewart, M.B., F.F.R.
Manchester

This paper gives an account of our experience in the use of wedge filters with 4 MV radiation in the treatment of carcinomata of the lower alveolus and of the antrum and accessory sinuses.

With conventional radiation, interest in wedge filter therapy in Manchester was small. The poor depth dose and the loss of wedge angulation created problems of prescription when treating at depth. Some of these have since been solved by Cohen (1959), but even so, from considerations of the differential absorption in bone, conventional therapy could never be a serious contender where alternative treatment by radium was available.

Following the introduction of 4 MV radiation, the position immediately changed. Theoretically at least, here was radiation with physical characteristics ideally suited for use with wedge filters. The relative absence of lateral scatter results in a more or less direct relationship between the dose at a point and the intensity of the primary beam through that point. Thus, attenuation of the primary beam, as by a wedge, is reflected accurately by the isodoses. The wedge angulation is thus maintained into depth.

From this same argument the depth dose at any point below an oblique surface is simply calculated, and the necessary correction for such obliquity may be incorporated in the prescription. Correction by use of bolus becomes less important, but may still be necessary in certain sites. In such cases a beam compensator such as that introduced by Ellis *et al.* (1959) might be used with advantage.

Despite the great advantage of skin sparing with megavoltage radiation, the danger of tumour involvement near the surface must be borne in mind. With 4 MV radiation in the treatment of tumours around the mouth, it is surprising how often bolus is necessary for this reason.

For the criteria of homogeneity and localization, a minimum requirement of three plain fields is necessary, these being arranged symmetrically around the head. With the increased penetration at 4 MV radiation, exactly the same conditions are achieved with only two wedged fields. Even so, for centrally placed tumours, wedge filter therapy can claim no advantage over cross-fire therapy with plain fields. For peripherally placed tumours, however, wedge therapy offers considerable advantage both in simplicity of prescription and in economy of radiation to normal tissues. It is from these theoretical considerations, to which may be added the general advantage of low differential bone absorption, that wedge filter therapy at 4 MV has come to play a substantial part in the treatment of head and neck tumours.

Three wedges of different slopes are in current use—40, 50 and 60 degrees. Considerations of the optimum shape of high dose zone coupled with the degree of surface obliquity dictate the choice of wedge angle.

The use of a variety of wedge angles facilitates the matching of the high dose zone to the tumour shape, thus reducing unnecessary radiation to a minimum. That this is desirable is generally accepted, but so sharp is the fall off at the edge of the treated zone that localization of the tumour must be exact, if it is not to be missed.

Inactive radon seeds are implanted as markers wherever possible and, following the preparation of a plastic beam direction shell, localization is verified radiographically. Prescription is then carried out on a contour taken from the shell.

Lesions of the Lower Alveolus

In the pre-megavoltage era, carcinomata of the lower alveolus were treated in a variety of ways. The small anterior lesion has shown very good results following treatment by a radium mould augmented by a submental radium beam field. Satisfactory results were also achieved on more posterior lesions using the radium beam cluster technique. Radon seed implantation, commonly used in older patients or patients with alveolo-faucial lesions, was rather less successful. Conventional beam direction was the standard radical treatment for lesions of the fauces, but was rarely used for lesions of the alveolus proper.

In the early experimental stage of megavoltage irradiation only very late cases were treated. More recently, 4 MV treatment of lesions of the posterior alveolus has become more routine, but anterior lesions are still, wherever possible, treated by radium mould plus beam.

The 4 MV wedge approach is illustrated in Fig. 1, using two fields, anterior and lateral. No build-up material is required unless there is extension into the cheek. Toward the further reduction of unnecessary tissue radiation, a block of dental compound, moulded to the

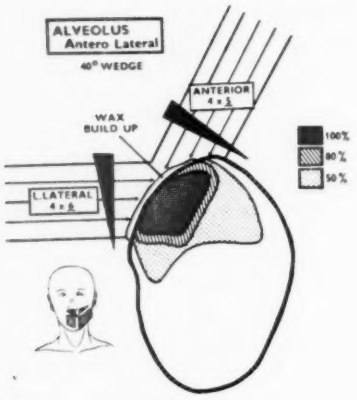

FIG. 1.

patient's bite, is worn during treatment in order to displace the tongue away from the high dose zone. This block serves the additional purpose of preventing any air gaps within the mouth.

Where the lesion extends anteriorly 40-degree wedges are used but where it is more posterior, a more suitable combined isodose plot is obtained with 50-degree wedges (Fig. 2). Reaction is thus confined to one side of the mouth, with consequent reduction of discomfort to the patient.

Tumour dosage during the early years ranged from 5,000–5,650 rads in three weeks. Mucosal reactions were in many instances very moderate and we may not have been using the whole of the biological tolerance available. During 1959 this dose has been increased to 6,000 rads in three weeks, without unduly severe reactions.

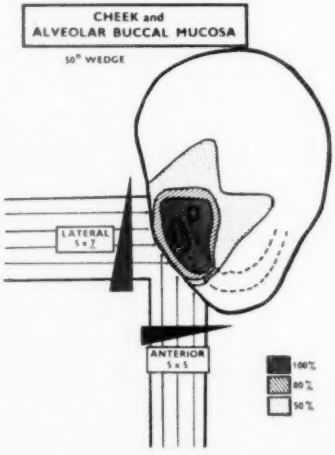

FIG. 2.

Lesions of the Antrum and Accessory Sinuses

Pre-megavoltage treatment of these tumours was reported by Gibb (1957). The megavoltage approach is inevitably dictated by the desire to spare the eyes. High dose conventional radiation of the eyes results in, first, the destruction of the conjunctiva and the cornea and, second, enophthalmos and cataract. It is perhaps worth while to separate the superficial and deep effects in this way, since, with 4 MV radiation, the former seldom occurs, provided that the eye is kept open during treatment. The latter may occur, but this normally does not give rise to pain. Thus the decision to irradiate an eye, when necessary, is made with much less emotional strain.

For treatment considerations, cases may be divided into two categories: A, where involvement is confined to structures below a horizontal plane through the roof of the antrum, and B, where there is extension above this plane.

A.—Treatment planning is simple. A wedge pair from front and side gives adequate coverage (Fig. 3). The superior edge lies just below the

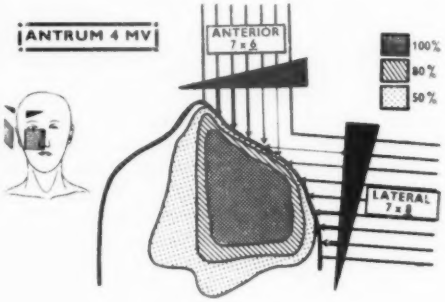

FIG. 3.

pupil of the eye to ensure clearance of the roof. The posterior border of the lateral field is positioned to cover at least the posterior wall of the antrum, but may be extended if there is evidence of involvement of the pterygoid fossa. The lower limit is dictated by cheek or mouth extension. The customary mouth block is used to keep the lower alveolus and tongue out of the high dose zone. Wax build-up is necessary, if there is extension to the tissues of the cheek.

B.—Where orbit, ethmoid cells or frontal sinuses are also involved, this approach cannot be accepted, because the eye on the sound side would be subtended by the lateral field. An anterior and superior wedge pair surmounts this difficulty (Fig. 4). On the debit side, however, is a relatively high dose in the frontal lobe, and care must be exercised that the postero-inferior

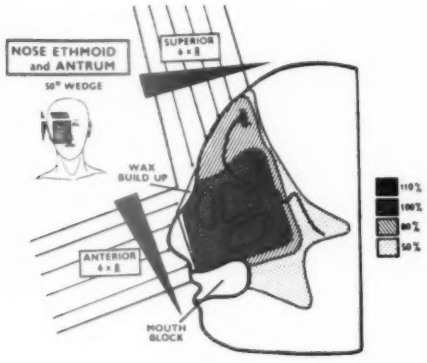

FIG. 4.

border of the high dose zone does not encroach on the mid-brain. Wax build-up over the ethmoid region is commonly necessary, and in such cases the front field is waxed up completely, thereby simplifying the prescription. A peep-hole is, however, preserved immediately in front of the pupil, so that the cornea may be spared from the anterior field.

In the special case where the tumour is restricted to the apex of the antrum but with lateral involvement of the zygoma and orbit, an alternative plan is possible. Two anterolateral fields, as shown in Fig. 5, may be arranged to

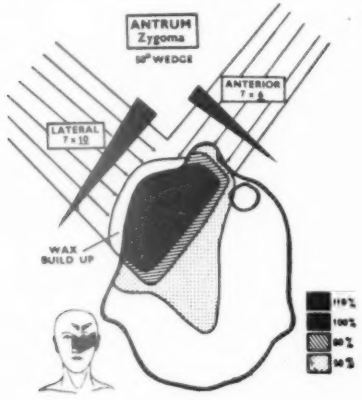

FIG. 5.

subtend the involved areas, yet miss the other eye. Such a treatment plan has an obvious weakness in the mid-line posteriorly, and has been used only in these rather restricted circumstances.

One further approach appears to have certain commendable features: The depth dose at 4 MV is relatively independent of area and odd-shaped fields are thus permissible. An L-shaped plain field from the front can be arranged to subtend frontal sinuses, ethmoid cells, nose and antrum, with no radiation to the eye. This single field has the natural disadvantage of falling dose posteriorly, but if this is boosted by a pair of parallel and opposed wedged fields from the sides, coming in behind the eyes, a relatively homogeneous high dose zone is achieved throughout the tumour volume without radiation to either eye. A cross section below the level of

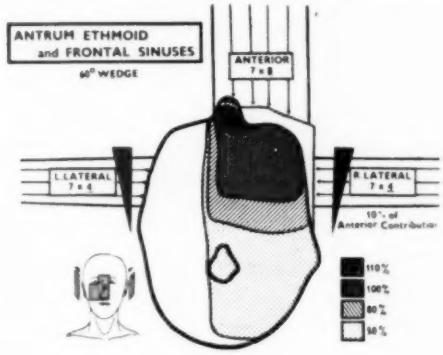

FIG. 6.

the eyes is shown in Fig. 6. It has the disadvantage of any single field approach—a rather high exit dose of the order of 60% tumour dose in brain. Over-enthusiastic and careless shielding of the eyes during treatment may be dangerous.

The early dosage, as with the alveolæ, ranged from 5,000 to 5,650 rads in three weeks, a larger proportion being treated at the lower level, in consequence of the larger volume. Again, such dosage was found to be tolerated well with little or no evidence of bone necrosis. Although it is as yet much too soon to assess necrosis risk, we have felt that this level was perhaps on the low side. The current practice is to give 6,000 rads in three weeks, where the treated volume is less than a 7-cm cube. Over this limit, 5,500 or 5,250 rads are given in three weeks, depending on size.

Results

During the experimental phase in 1955, the intent was almost wholly palliative; all cases in that year have therefore been excluded. Radical treatment for patients who would previously have had palliation, plus the selection of early lesions for treatment by well tried radium methods, makes any valid comparison extremely difficult. The fairest comparison that may be made is between radical wedge filter cases in the years 1956 and 1957, and the overall results in

the years 1950 to 1954. These are assessed for survival at two years and also for primary recurrence at two years or at death within that period. The results are given in Tables I and II. From the figures of primary recurrence

TABLE I.—ALVEOLUS

	No. treated	2-year survival	Primary recurrence at two years or death within that period
All cases 1950–54 ..	108	57%	45%
4 MV wedge therapy radical 1956–57 ..	21	(48%)	(33%)

TABLE II.—ANTRUM AND ACCESSORY SINUSES

	No. treated	2-year survival	Primary recurrence at two years or death within that period
All cases 1950–54 ..	136	31%	60%
4 MV wedge therapy radical 1956–57 ..	21	(38%)	(47%)

there may be some suggestion of improvement. The fact that this is not reflected in the survival rate for the alveolar cases is explained by death from metastases or other causes. However, numbers are too small to arrive at any valid conclusions and at this stage there is neither evidence for nor against this mode of treatment.

Thus, in conclusion, wedge filter techniques with 4 MV radiation offer a precision and elegance of prescription hitherto not available. In consequence reactions are more localized and treatment more easily tolerated by the patient. Although as yet no conclusions may be drawn from results, it is hoped that, given optimum dosage, the increased proficiency of technique afforded by wedge filter therapy will express itself in the form of better results.

REFERENCES

COHEN, M. (1959) *Acta radiol., Stockh.*, **52**, 65, 158.
ELLIS, F., HALL, E. J., and OLIVER, R. A. (1959) *Brit. J. Radiol.*, **32**, 421.
GIBB, R. (1957) *Proc. R. Soc. Med.*, **50**, 534.

The Treatment of Carcinoma of the Middle Ear by the 4 MV Linear Accelerator

By K. S. HOLMES, M.B., D.M.R.T., F.F.R.
Manchester

FIVE years ago Boland and Paterson (1955) presented to this Society a report on the treatment of carcinoma of the middle ear at the Christie Hospital and Holt Radium Institute, Manchester. At that time the 4 MV linear accelerator became available for routine clinical use and it is now possible to review the treatment of this disease by the linear accelerator and to compare the results with those obtained by methods other than supervoltage.

In order that the present position may be understood fully, it is of advantage to summarize the way in which cancer of the middle ear has been treated in the past at the Christie Hospital. From 1932–1937, the middle ear was exposed at operation and a radium tube of 2 to 5 mg inserted. A dose as high as 5,500 r at 1 cm from the tube was achieved, but the fall off in dose beyond this distance was so rapid that it was impossible to irradiate a sufficiently large volume. This disadvantage was overcome by the use of multi-field beam directed X-rays of 250 or 500 kV, and the majority of patients have been treated in this way. One dominant field was balanced by four to six contralateral fields. A tumour dose of 5,000–5,500 r was given in three weeks, or its equivalent dose in five weeks. Better results were obtained by the lower than by the higher of these two dose levels.

Boden (1950) reported a few patients in whom late radiation damage to the brain-stem occurred after treatments of this kind. In 7 patients with damage, the dose in the brain-stem from small fields was between 4,500 and 6,050 r in three weeks. He suggested that 4,500 r in three weeks was the upper limit of safety in the brain-stem.

The middle ear being a cavity in bone made the use of harder radiation desirable, and some patients were later treated by a 10-g radium beam unit. A cluster of three fields from the affected side gave a tumour dose of 4,800–5,500 r in three weeks. Unfortunately, the percentage depth doses from the 10-g beam are low and it was difficult to attain a sufficiently high dose in the deepest part of the irradiated zone.

The physical characteristics of 4 MV X-rays are such as to overcome all the disadvantages of these previous methods. Because of the quality of the beam there is very little differential absorption in bone, while the high percentage depth doses ensure adequate radiation of the whole of the treated volume. In addition, the treatment is made more tolerable by the mild skin reactions. For these reasons, and because the number of patients seen is so small, a trial series by random selection to compare the results of conventional X-rays or radium beam with those of supervoltage was not undertaken when the 4 MV linear accelerator came to be used clinically. Rather it was decided that all cases deemed suitable for radical treatment should be treated by this 4 MV machine. This policy has been consistently followed since then.

Technique.—The technique of treatment on the linear accelerator remains essentially un-

changed from that by beam directed X-rays of conventional levels. The history, the findings of the surgeon at operation (if anything more than a biopsy has been done), a clinical examination and radiographs all contribute information as to the position and spread of the tumour. Nevertheless, it must be admitted that in the majority of cases it is impossible to localize the tumour with exactitude, particularly as the spread in bone may not be apparent radiographically. Moreover, many of these patients have chronic middle-ear infections which make radiological diagnosis difficult. For this reason the treated volume must be larger than may seem at first necessary and, at a minimum, the whole of the petrous temporal bone is included.

The technique of beam direction itself is here described in outline only. A Perspex shell is fitted to the patient's head. The volume to be treated is chosen and localized with radiographs in respect to the shell. Verification films check the final position. Field selection follows on this. Three fields are found to give an ideal dose distribution. One homolateral field directed along the axis of the petrous temporal bone is balanced by contralateral submandibular and temporal fields. This arrangement enables the whole of the petrous temporal bone to be included in the treated volume while the midbrain lies posterior and is spared. In order that the skin dose is as low as possible, the Perspex is cut away coincident with the entrance beams. However, if the tumour involves skin or has grown to the external auditory meatus, it is necessary to build up the whole or part of the dominant field with wax of 1 cm in thickness. The dose then attains its 100% level on the skin. Field sizes vary, but usually are of the order of a 6-cm circle. A tumour dose of 5,000–5,500 rads is delivered in three weeks.

A few patients have been treated by two fields with wedge filters and directed from the affected side. A similar volume is irradiated and the tumour dose remains the same as for the three field arrangement.

Material.—Between 1932 and 1958, 115 pathologically proved cases of carcinoma of the middle ear were seen at the Christie Hospital (Table I). The following cases have been

TABLE I.—CASES SEEN 1932–1958

Treated radically	78
Treated palliatively	22
Not treated	15
Total	115

excluded from this series: (1) All those lacking definite pathological proof of malignancy. (2) All basal cell carcinomas. (3) All glomus tumours. (4) All tumours considered to be truly arising in, or localized to, the external auditory meatus. There is often great difficulty in differentiating these meatal tumours from those which arise in the middle ear itself.

Pathology.—The histology is shown in Table II.

TABLE II.—HISTOLOGY

Squamous-cell carcinoma ..	102
Carcinoma	5
Transitional cell carcinoma ..	3
Adenocarcinoma	3
Anaplastic carcinoma	1
Secondary carcinoma ..	1
Total	115

Further information is not available on those designated merely "carcinoma". The secondary carcinoma was metastatic to a primary in the breast; it was not treated.

Results.—The five-year results of all cases treated are shown in Table III. Treatments

TABLE III.—ALL CASES TREATED RESULTS AT 5 YEARS

No. of cases	% alive
71	21%

were by a radium source, by beam directed X-rays of 250 or 500 kV and by the radium beam. To date there are no cases treated by supervoltage at five years. 18 of these 71 patients were treated palliatively and only one of those 18 survived for five years. This is a large series of a rare disease. The figure of 21% compares favourably with the isolated survivors reported in most other series and is an advance of 4% on Boland's figure for the Christie Hospital results five years ago.

Table IV shows those patients treated radically

TABLE IV.—CASES TREATED RADICALLY RESULTS AT 5 AND 2 YEARS

	No. of cases	% alive
At 5 years ..	53	26%
At 2 years ..	53	32%

and compares the results at two and five years. The same 53 patients are compared at the two periods. It can be seen that there is a difference of only 6% between the two- and five-year survival rates. The 6% is equivalent to 3 deaths. The primary recurred locally in 2 whilst the third died of myocarditis. As it is proposed to compare certain two-year survival rates this small difference between the two- and five-year rates is noteworthy.

It is now possible to compare the results of three methods of treatment (Table V). The results at two years are shown of patients treated radically by beam directed X-rays, by the radium beam and by the 4 MV linear accelerator. The figure of 55% for the radium beam is from 11 cases only but represents a marked increase over the 30% obtained by

TABLE V.—CASES TREATED RADICALLY. RESULTS AT 2 YEARS

		No. of cases	% alive	
Pre-supervoltage	Beam directed X-rays ..	37	30%	35%
	Radium beam	11	55%	
4 MV linear accelerator		22		77%

beam directed X-rays. There is a further increase to 77% for the 4 MV cases. When the beam directed X-rays are added to the radium beam cases a "pre-supervoltage" group is formed. The survival rate at two years for this group is more than doubled by those treated by supervoltage.

It has already been said that five-year figures are not yet available for supervoltage. However, it has also been shown for all radically treated patients, that there is a difference of only 6% between the two- and five-year survival rates. As there is no reason to suppose that the pattern of survival will change with the new treatment, the relationship between the supervoltage cases at two and five years should remain the same as before.

The increase from 35% for the pre-supervoltage group to 77% for supervoltage (or 4 MV) is so striking that doubt may arise as to the validity of the comparison. Evidence is given below to show that the two groups are very similar in their composition.

Age.—The mean age of the pre-supervoltage group was 57 and of the 4 MV group 56.

Pathology.—The proportion of squamous cell carcinomas in each group was 88% and 82% respectively.

Involvement of bone.—Radiographic evidence of bone destruction was found in 57% of the pre-supervoltage group and in 50% of the 4 MV group.

Selection of cases.—The percentage treated radically of all patients seen is shown in Table VI.

TABLE VI.—SELECTION OF CASES

	Pre-supervoltage	4 MV
Number of cases seen	78	27
Number treated radically	48 (62%)	22 (81%)

It will be remembered that only those patients treated radically are included in the two groups. The figures of 62% for the pre-supervoltage group and 81% for the 4 MV group show that there has been no bias towards selecting only a few of the total group seen for treatment on the supervoltage machine. Rather the tendency has been to accept patients for the accelerator who had more advanced disease than previously would have been considered for radical treatment. This trend has been noticed in diseases other than cancer of the middle ear in relation to supervoltage treatment.

Therefore, it is likely from these comparisons that the two groups are similar in regard to the material which constitutes them and that those treated by supervoltage do not form a selected series of early cases.

Conclusions.—Thus the evidence is strong that the treatment of carcinoma of the middle ear by the 4 MV linear accelerator does represent a significant advance over that by other methods. It is hoped and expected that when five-year figures become available, there will be a marked increase in the percentage of survivors.

REFERENCES

BODEN, G. (1950) *J. Fac. Radiol., Lond.*, **2**, 79.
BOLAND, J., and PATERSON, J. R. (1955) *J. Laryng.*, **69**, 468.

Bladder Carcinoma

By R. C. S. POINTON, F.F.R.
Manchester

THE bladder is a relatively deep-seated organ, mainly surrounded by bone, lying in close relation to the other pelvic organs; moreover, tumours of the bladder are of limited radiosensitivity and require high doses if cure is to be obtained. Even with the use of elaborate multifield and rotational techniques, treatment with conventional 250–300 kV X-ray therapy is difficult and entails the production of severe reactions to deliver an adequate tumour dose. Before the introduction of the 4 MV linear accelerator, the majority of radical X-ray treatments of bladder tumours at the Christie Hospital were carried out on a 500 kV constant potential machine of H.V.L. 6·3 mm Cu. With this quality of X-irradiation, the bone shielding was significantly less than with conventional 250–300 kV irradiation and not greatly different from 4 MV irradiation. Even so, to deliver an adequate dose at the bladder required the use of a complex multifield treatment technique.

When introducing a new machine into routine clinical practice, the method of use will be influenced mainly by past experience with the

type of lesion to be treated, and what evidence, both clinical and experimental, has accumulated during the trial period before its acceptance into routine use. As experience increases, alterations and adjustments will be made as the treatment technique develops. Once the technique and dosage has been established, the method of comparison of results has to be determined.

The routine use of the linear accelerator for the radical treatment of bladder tumours was begun in 1955; I shall discuss our experience in the first two years of its use and present the results of patients treated in 1955 and 1956 as assessed at three years. All patients were treated with the same technique and to the same dosage levels.

The selection of patients for treatment was as follows: All early bladder carcinomata, i.e. mucosal and muscular tumours up to a circle of 4 cm diameter, were treated by means of permanent radon seed implants, and this policy has been rigidly adhered to. Metastatic tumours and tumours with gross pelvic fixation were treated palliatively. The remainder, including multiple mucosal tumours, were treated radically provided that the general condition was adequate. This group included both untreated patients and recurrent and residual tumours following surgery.

Bladder tumours are of limited radiosensitivity, and the principle of small volume high dose has been adhered to. No deliberate attempt was made to treat the whole bladder except when there were multiple tumours involving most of the surface of the organ, nor was any attempt made to include the regional lymph nodes in the treatment volume. The field sizes used were 8 × 6 cm or the equivalent area for small lesions and 10 × 8 cm or the equivalent area for larger lesions.

For this type of treatment accurate localization of the tumour is essential. Localization is based on the combination of the cystoscopic and examination under anæsthesia findings, and the use of cystograms. The best method of localization is undoubtedly to insert inactive gold seeds cystoscopically to demarcate the limits of the tumour; furthermore, if this has been done, verification radiographs through one of the treatment fields taken either on the linear accelerator or a simulator unit can be made. Failing this, the usual cystograms are made using a weak barium suspension as the opaque medium. The position of the tumour relative to anterior and posterior skin markers is determined.

The treatment technique adopted was a 3-field symmetrical arrangement with 1 anterior field and 2 posterolateral fields. Beam direction was carried out as follows:

There is no actual pin and arc on the linear accelerator but by virtue of its design to rotate isocentrically the machine acts as its pin and arc. The linear accelerator is designed to rotate about a point 1 metre from the focal spot. Thus if the tumour is placed 1 metre from the focal spot then the machine rotates about the tumour. Even with the linear accelerator, it is still felt that compression is worth while and to obtain this we use a telescopic Perspex applicator on which the F.S.D. can be read. The end of the applicator is closed by a sheet of 3 mm Perspex which does not greatly diminish the skin sparing effect of a 4 MV irradiation.

For fields of area up to 50 sq. cm, the dose given was 6,000 rads and for areas up to 80 sq. cm 5,500 rads in three weeks.

In the years 1955–1956, 87 patients were treated radically on the linear accelerator, of whom 60 were previously untreated, and 27 recurrent or residual. 83% were histologically proven.

Of the 87 treated, 25 or 29% are alive at three years; of these, 22 were histologically positive: one has had a total cystectomy (Table I). In the years 1953–1954, that is pre-megavoltage, 97 bladder tumours were treated with radical X-ray therapy with a three-year crude survival rate of 27%. Fig. 1 shows the survival curves for the two groups, i.e. 1953–1954 pre-megavoltage treatment, and 1955–1956 4 MV X-ray therapy,

TABLE I.—RADICAL TREATMENT OF BLADDER TUMOURS
Results of Cases Treated by 4 MV Linear Accelerator 1955–56

Type of case	No. treated	Three-year crude survival rate
Previously untreated/recurrent ..	87	29%
Previously untreated..	60	28%

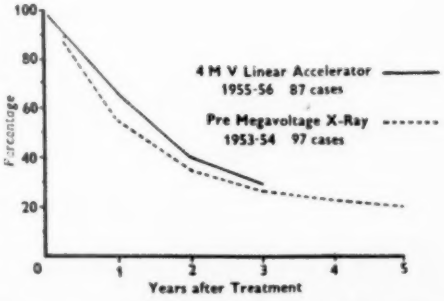

FIG. 1.—Radical treatment of bladder tumour. Crude survival rates.

and as can be seen there is no great difference between the two curves. If we consider the years 1955 and 1956 separately, and compare them with the pre-megavoltage group, the results are as seen in Table II. The numbers in

TABLE II.—RADICAL TREATMENT OF BLADDER TUMOURS
Results of Previously Untreated/Recurrent Cases

Year	Type of treatment	No. treated	Three-year crude survival rate
1955	4 MV linear accelerator . .	45	22%
1953–54	Pre-megavoltage X-ray . .	97	27%
1956	4 MV linear accelerator . .	42	36%

the two megavoltage groups are small and the difference in the results in these groups is not statistically significant in the orthodox sense, although they show promise. Retrospective staging of the cases in the two years involved did not indicate that the criteria of selection had altered between them. The only change in technique was a slight increase in the field sizes used. It would seem probable that the difference is due to more familiarity with the machine and possibly to improvement in localization methods.

Symptoms due to bladder reactions have not been severe. It has been exceptional for a patient to have much dysuria or strangury during treatment. Clinical impression was at first that the symptoms were less than was found with the 500 kV cases, but I do not think there is any significant difference.

A small number of 4 MV and 500 kV treated patients were cystoscoped at varying periods after completion of treatment in an effort to compare the bladder mucosal reactions; however, nothing conclusive came of this investigation.

Unless the tumour is very anteriorly placed, it is difficult not to produce some degree of rectal reaction on treating a bladder tumour radically with external irradiation. The severity of the symptoms varies from patient to patient. Clinical impression has been that the degree of reaction with the 4 MV radiation has been less severe than with 500 kV X-ray, as might be expected from the field distribution and the smaller volume of the pelvis raised to high dose.

In this series of 87 patients, there has been one example of severe bowel injury:

Male, aged 70. Cystoscopy revealed on the posterior wall of the bladder a solid nodular tumour 4–5 cm in diameter; the margins were ill-defined. Per rectum the prostate was very hard and suggestive of a carcinoma on left side; a tumour was palpable on the posterior wall of bladder, forming a plaque 5 cm in diameter. Treatment was given on the linear accelerator, using 8 × 8 cm fields to a dose of 6,000 rads in three weeks. Towards the end of the course he developed diarrhœa, which continued after the completion of treatment. Sigmoidoscopy approximately one month later revealed that at 10–15 cm the rectal wall was indurated and the instrument could not be passed further. Diarrhœa persisted, and two months after completion of treatment he developed signs of peritonitis and died. Autopsy revealed perforation of a necrotic area of pelvic colon.

No other case of large or small bowel injury occurred in this series.

So far we have not observed any evidence of late complications such as severe bleeding from telangiectasia or contracted bladder. These late complications are in our experience uncommon with external irradiation of bladder tumours.

In the first two years of the routine clinical use of the linear accelerator in the treatment of bladder tumours, a treatment method was evolved which has proved easy to use, and which has enabled radical treatment without the production of severe reactions or complications. The early results would seem to support the contention that with the introduction of a new machine producing radiation, the relative biological efficiency of which is not fully known initially, the results will not be better than those obtained with well-established, orthodox treatment. As experience with the clinical use of the machine increases, results should improve.

With the acceptance of an R.B.E. of 85 : 100, the dose was increased in 1957 so that for fields of area up to 50 sq. cm the dose became 6,500 rads, and for the larger fields 6,000 rads in three weeks. With these dose levels, there has been no noticeable increase in the severity of reactions, nor have any significant complications occurred.

In order to compare the results of 4 MV treatment with 500 kV treatment of bladder tumours, it was decided to run a clinical trial. In view of the number of variables, a properly conducted random selection trial was decided upon. For the past three years, untreated cases of bladder tumours suitable for radical X-ray therapy have been divided into two groups, one group receiving 500 kV irradiation, and the other 4 MV irradiation. This trial has not been running long enough to report on.

To summarize, with the 4 MV linear accelerator, radical X-ray treatment of bladder tumours has become simpler and less wearing to the patient. Initial results of treatment have been satisfactory, but a full assessment in comparison with the previous method of treatment depends on the findings of the random selection trial now proceeding.

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Section of Otology

President—RONALD MACBETH, D.M., F.R.C.S.

Meeting
December 4, 1959

DISCUSSION ON THE USE AND ABUSE OF ANTI-BACTERIAL DRUGS IN OTOLOGY

Dr. Mary Barber (London) opened the discussion with a review of the bacteriology of acute otitis media and stated that the majority of cases were infected with Gram-positive cocci, notably *Streptococcus pyogenes* and *Diplococcus pneumoniæ*. Since practically all strains of these species had remained sensitive to penicillin this was the drug of choice for treatment of acute otitis media.

She discussed the pattern of the development of resistance of organisms to antibiotics in different parts of the world, and made suggestions for the management of the problem of resistant strains of pathogenic organisms. She finally raised the question of the desirability of treating all children suffering from acute sore throats with penicillin in order to prevent the possible development of otitis media.

Dr. P. A. Walford (Felsted, Essex):

Are Antibiotics Really Desirable in Treating Otitis Media?

Definition.—Unless otherwise stated, otitis media in this paper does not mean the discharging ear but the ear with an intact drum, whether red and bulging or just pink. The acute discharging ear presents no great problem in treatment, but when confronted with a bulging drum is it permissible to use antibiotics without letting the pus out? Is it permissible to delay giving an antibiotic until the drum has ruptured, and will the result of such treatment be as good as if paracentesis had been done? I speak as a general practitioner who finds it impossible to summon an anæsthetist and do a paracentesis. Since 99% of cases of otitis media are treated by general practitioners and 1% by consultants, we practitioners look to the consultant for advice on how we should treat these patients and not how he would treat them.

If we give antibiotics will the result be a middle ear full of sterile pus that organizes later to produce deafness or will the pus drain through the eustachian tube? If we do not give antibiotics will acute mastoiditis develop in 12% as was found by Abercrombie (1957) in pre-penicillin days, or have the organisms decreased in virulence? I am sure that they are less virulent. Even in the 1940s, before penicillin, Butler (1948) treated 461 cases of purulent otitis media without sulphonamides (having previously done a controlled trial) and only two required mastoidectomy. The improved results are due both to penicillin and to decreased virulence of the organisms.

To revert to the bulging drum, is it wise to treat it with penicillin without paracentesis? In 1948 Young and Simson Hall treated 46 bulging drums in this way without ill effect and in 1958 Dixon reported a similar series. But it is one thing giving regular penicillin injections in hospital, and quite another handing the mother a bottle of oral penicillin and trusting her to give it when she remembers or when the child agrees to take it. Everyone knows how difficult it can be to persuade children to take medicine and I have no doubt that once the earache has stopped many mothers give up the struggle. 9 out of 10 children are given their penicillin by mouth (Wheatley, 1958) and I doubt whether many receive it for more than two days.

What is the result of this treatment? To find this out we must turn to the Medical Research Council Survey of 1957 carried out on otitis media for a year by 28 general practitioners. They saw, in all, 1,300 cases and as the majority received penicillin, the results were hailed as a triumph for its use, although, as Fry (1958) pointed out, those practitioners who used penicillin in only a minority of their cases seemed to get just as good results. Only 1 paracentesis was performed in these 1,300 cases. 1 case of mastoiditis required operation. However, 35 patients (3%) were left with perforations dry or moist. This cannot be laid at the door of antibiotics for if there is one thing you can do with antibiotics it is to prevent the chronic perforation and it looks as if these patients were not given big enough doses of the correct antibiotic. The chronic perforation may be impossible to heal but I believe the acute perforation will always heal with the right antibiotic provided the perforation is not allowed to be partially blocked by debris. I do not think there is any place for local antibiotics in this condition.

Deafness.—If the figures for deafness are corrected by omitting the 400 babies and infants under 5 who could not have had their hearing tested satisfactorily, the incidence of deafness works out at nearly 10%. Unfortunately the

method of testing was left to individual doctors: presumably most of them used some form of whispering test but we do not know at what distance. Clearly the testing was crude and the figure is therefore too low, but it is impossible to compare it with any other series. I personally believe that it is much higher than the figures I have found in my patients in whom I try to avoid antibiotics, but as the figures are not comparable this is no more than an opinion. Fry (1958) who used antibiotics on only 15% of his unperforated patients found a deafness rate of less than 1% in 422.

Quite a few authors have blamed penicillin for causing deafness, notably Popper (1957) who reported 93 such cases. Persky (1957) blamed inadequate dosage and Rutherford (1956) noted, as others have done, the tendency to relapse after stopping penicillin.

The tendency to relapse is probably responsible for some deafness: all authors agree that the more often their patients relapse, the more likely they are to become deaf. Relapses are more frequent with oral penicillin than with intramuscular therapy, even when patients are treated in hospital (Schmidt, 1958). Serous otitis is said now to be more common (Persky, 1957) and much of it is being blamed on penicillin. It is not known for certain whether the deafness of untreated serous otitis is permanent or not.

Antibiotics other than penicillin are used in otitis media but not extensively: I do not know any published series big enough to show whether they avoid the disadvantages of penicillin.

Obviously I do not advocate abandoning penicillin altogether for otitis media; how is one to decide to whom it should be given? When I looked through my own records the other day I found that the severity of the illness had prompted me to give it in only 4%. Nearly always the reason was that the otitis media was complicated by some other illness such as acute follicular tonsillitis or pneumonia.

My own custom is this: with the exceptions I have mentioned, whatever the drum looks like, I give 1% ephedrine and glycerin ear drops (Ogilvy Reid, 1946). In 90% this takes the pain away rapidly; in the 10% in whom pain remains after twenty-four hours penicillin is given. Should perforation occur, the drops are continued plus the appropriate antibiotic. It is vital to have the discharge stop within a fortnight if deafness is to be avoided (Poulsen, 1950) and if the discharge continues beyond a week, the ear is very gently syringed: this works like a charm by clearing away the debris blocking the perforation and the discharge invariably stops after a couple of days.

In summary, an increase in minor degrees of deafness is the price we are paying for having eliminated mastoiditis. Much deafness could probably be avoided by giving penicillin to selected rather than all cases. However, I have to admit that this is partly conjecture because there have been no controlled trials on which to base such an opinion; nor are there likely to be, for such a trial would need to be not on the 1% of failures referred to the consultant but on the 99% of early cases seen by the general practitioner. So the trial would need to be conducted by general practitioners but as the hearing tests would have to be audiometric it is difficult to see how such a trial could be constructed at the present time.

REFERENCES

ABERCROMBIE, G. F. (1957) *Proc. R. Soc. Med.*, **50**, 409.
BUTLER, H. (1948) *Ann. Otol. Rhin. Laryng.*, **57**, 992.
DIXON, J. W. (1958) *J. Laryng.*, **72**, 227.
FRY, J. (1958) *Brit. med. J.*, ii, 883.
Medical Research Council (1957) *Lancet*, ii, 510.
PERSKY, A. H. (1957) *Amer. Practit.*, **8**, 489.
POPPER, O. (1957) *S. Afr. med. J.*, **31**, 54.
POULSEN, I. P. V. (1950) *Acta otolaryng., Stockh.*, **38**, 120.
REID, W. O. (1946) *Brit. med. J.*, i, 648.
RUTHERFORD, M. (1956) *Eye, Ear, Nose, Thr. Mon.*, **35**, 571.
SCHMIDT, M. R. (1958) *Acta otolaryngol., Stockh.*, Suppl. 140.
WHEATLEY, D. (1958) *Brit. med. J.*, ii, 907.
YOUNG, A., and HALL, I. S. (1948) *J. Laryng.*, **62**, 551.

Mr. John H. Otty (Bradford):

A leading article on the progress of chemotherapy in the *British Medical Journal* of February, 1939, stated "the location of the disease is of far less consequence than the identity of the responsible micro-organism. A knowledge of the varied capacity for evil of the hæmolytic streptococcus is a useful asset from this point of view; besides many more obvious indications which it affords, it will, for example, suggest sulphanilamide or preferably M & B 693—since a pneumococcus is sometimes concerned—be tried in all cases of otitis media and mastoiditis".

Shortly after this article appeared I was called out in the North of Scotland to see a man aged 43, who had had pain in the right ear for three days. The tympanic membrane was dull, red and bulging and I thought I could see pus in the middle ear. I did a myringotomy and obtained pus, which I swabbed and from this a profuse growth of pneumococcus Group B was obtained. I advised that the man be given M & B 693. Some five weeks later the doctor was enquiring about another patient and I asked after Mr. G.—"Oh he is very well but he still has a little discharge". I was unhappy about this since the man lived nearly seventy miles from Aberdeen

and, after a certain amount of persuasion, the doctor agreed to send him in to see me.

The patient's story was that all went well for a week or ten days and the ear dried up completely. After a short bout of pain the ear began to discharge again and had continued to discharge more or less continuously thereafter. On examination there was an obviously active suppurative otitis media with sagging of the postero-superior meatal wall. There was no mastoid tenderness. X-ray showed "marked decalcification with loss of translucency—the result of mastoiditis". At operation the whole mastoid was grossly infected and the whole tip came away almost like a sequestrum. This was my first experience of masked mastoiditis and it made me cautious about using sulphonamides in otitis media. After this I saw numerous similar cases which had been treated with sulphonamides.

Early in 1946 penicillin, in small amounts, was made available for civilians. A small series of cases of otitis media in adults was treated with sulphathiazole and another with penicillin. From this small series it was evident that penicillin, in the small doses we were using, was the more effective. Sulphathiazole was used in a fairly large dosage of up to 35 g in three and a half to five days. Penicillin was at this time given in a dosage of 15,000 to 20,000 units three-hourly. Of 15 cases treated with sulphathiazole, 9 required mastoidectomy (7 of these were caused by hæmolytic streptococcus). Of 32 patients treated with penicillin, only 4 required mastoidectomy.

Early in 1947 penicillin was more freely available and after I came to Bradford its use became routine in the treatment of acute otitis media.

Between March 7 and May 27, 1947, 37 patients with otitis media and suspected mastoiditis were treated by myringotomy and intramuscular penicillin—in none of these was mastoid operation necessary—all the ears healed and became dry. At this time we were still giving 20,000 units intramuscularly three-hourly.

Later I found that by giving one mega unit of penicillin intramuscularly the pain was strikingly relieved, so much so that I began to wonder if myringotomy was really necessary and I stopped doing it, or having it done, on my patients. The results seemed to be eminently satisfactory and instead of giving the patient three-hourly injections the routine became one mega unit on admission and 500,000 units night and morning. We still obtained good results and the vast majority of ears were healed, dry and almost normal in appearance, in from five to seven days. Our registrar was still doing myringotomy, on the insistence of my colleague and friend, the late Donald Watson; he could see little difference in the time of healing of Donald Watson's cases and mine, so we suggested that he review those who had myringotomy done and those who had not, to see if there was any difference in the residual deafness. There was none, and so now it is the exception rather than the rule for myringotomy to be done.

I have reviewed some 133 unselected cases of otitis media treated as acute otitis media by myself and my colleagues Stephen Kavanagh and H. M. Jones in the years 1954-1958. These are not all the patients treated.

Of the 133 treated, only 13 failed to resolve. Of the failures, 10 on review were really cases of chronic suppurative otitis media. One patient had suppurative otitis media for five weeks before admission; since 100,000 units of penicillin six-hourly for forty-eight hours produced no appreciable improvement, a cortical mastoid operation was done. Another ear became dry with penicillin after two days, but relapsed; at operation cholesteatoma was found—probably due to chronic suppurative otitis media from the beginning. The third patient was treated with 500,000 units of penicillin six-hourly, but the tympanic membrane was not normal after three weeks, so a cortical mastoid operation was done. This patient had previously been treated with sulphonamides.

I have had little experience of the use of oral penicillin. I have always been doubtful as to whether it was possible to reach a bactericidal level of the drug in the blood. We abandoned the use of procaine penicillin because of the difficulty in cleaning the syringes and because the injection was by no means painless; I have not tried the new long-acting drugs, such as Triplopen. I had formed an impression that oral penicillin was responsible for many of the failed cases which we occasionally saw, and that it was probably responsible for the rather rare cases of acute mastoiditis we see nowadays, but examination of records has not been helpful in this respect.

I have studied the records of the emergency mastoid operations at the Royal Eye and Ear Hospital, Bradford for 1954-1958. There were 53 emergency operations, of which 33 were for acute exacerbation of chronic suppurative otitis media. In 6, simple incision through the mastoid swelling down to the bone (Wild's incision), and intramuscular penicillin, was all that was necessary to obtain complete resolution. In only 14 was the classical cortical operation necessary.

5 chronic cases complicated by meningitis recovered with penicillin intramuscularly and sulphadiazine and sometimes penicillin intrathecally. 2 patients had cerebellar abscess, 1 died; 9 had temporosphenoidal abscesses, 2 died.

The abscess was usually treated by aspiration and injection of penicillin.

When penicillin was made freely available we found general practitioners prescribing penicillin ear drops for any discharging ear. I do not think they ever did good—they certainly increased the number of cases of dermatitis of the meatus and pinna. Fortunately they seem no longer popular.

Lewis and Gray (1951), writing on the treatment of chronic otorrhœa with chloramphenicol, suggested that the variety of organisms found in chronic suppurative otitis media made the use of local penicillin irrational. Since streptomycin rapidly produces resistant strains, it should be excluded. Chloramphenicol is stable and neutral and is effective against a wide range of organisms. It is soluble in propylene glycol which is non-toxic and miscible with water and is hygroscopic. 15% chloramphenicol in propylene glycol, a saturated solution, was used. I have tried this chiefly in discharging fenestration and radical mastoid cavities, but having had several patients develop sensitivity, not easy to soothe, I now use it only occasionally.

I have not used antibiotics to any extent for the treatment of chronic suppurative otitis media, since I believe the treatment of this condition is largely surgical, due to irreversible changes in the mucosa of the middle ear or the bone of the mastoid. If conservative measures are to be tried, I still believe that routine efficient toilet of the meatus and the middle ear is of paramount importance, and that boric and spirit drops are as effective and much cheaper than drops containing antibiotics.

I have used antibacterial drugs very little in the treatment of skin conditions which affect the ear. Most of my patients with external otitis respond favourably and quickly to efficient cleansing of the meatus, boric and spirit drops and 1% hydrocortisone ointment to relieve irritation. Furunculosis responds most rapidly to penicillin intramuscularly.

To sum up, I would suggest that in otology, penicillin by intramuscular injection is the treatment of choice in acute suppurative otitis media. It is invaluable in the treatment of the complications of aural suppuration and its effectiveness may be enhanced by the use of one of the sulphonamides. If the organisms are insensitive to penicillin, then another appropriate antibiotic may be used, but I have been surprised how often patients have recovered following treatment with penicillin when the organism was reported as insensitive. It is doubtful if antibacterial drugs or antibiotics have a place in the treatment of chronic suppurative otitis media. Antibiotics and antibacterial drugs should not be used by local application and I doubt the wisdom of giving small doses of sulphonamides or antibiotics over weeks, months or even years as a prophylactic since it may lead to organisms becoming resistant to these drugs.

REFERENCES

Brit. med. J. (1939) i, 340.
LEWIS, R. S., and GRAY, J. D. (1951) *Brit. med. J.*, ii, 939.

Dr. T. A. A. Hunter (Marlborough) said that he always had in mind the contrast between conditions before the war and those since. Before the war otitis media was a reason for anxiety. The myringotome was an essential item of a practitioner's equipment; discharging ears were a commonplace and there was never absent from one's mind the dread possibility of an acute mastoid with its sinister possibilities. Since the war as medical officer of a public school he had treated between 20 and 30 cases of otitis media annually. In only one had there been a failure of resolution in the pre-suppurative phase and that had been inherited from a previous school. As a school doctor he had the best of both worlds: he saw his cases as early or even earlier than the general practitioner and could treat them with nursing assistance under hospital conditions so that there was no administrative difficulty about injections. Routine treatment was the immediate administration of one and a half mega units of Duracillin intramuscularly followed by two capsules of Penicillin V four-hourly (missing night doses) until the drum was normal. It was most exceptional for this to take more than two or three days. Admittedly this was big dosage but it produced results and he suggested that much of the criticism that had been levelled at penicillin was due to insufficient initial dosage and the failure to maintain a constant effective blood level over a sufficient time. Although in theory oral penicillin could be effective, in practice it was likely to produce both these errors. He declared himself undeterred by the bogy of penicillin sensitivity. It was a rare condition and the risk of its occurrence was infinitely less than tne risks of serious complications in otitis media untreated by antibiotics.

Dr. I. Simson Hall (Edinburgh) said that Dr. Walford had raised the question whether it would not be better to withhold antibiotics in certain cases of acute otitis media. To get an idea of the implication in such a question it was necessary to understand something of the natural history of the disease when antibiotics were not used. Taking figures from an article published just before the introduction of chemotherapy it appeared that out of 189 patients

having mastoid operations 28 had paracentesis, but out of 221 with paracentesis only 28 came to mastoid operation. Obviously, therefore, the safety in this disease lay in relief of the suppuration by myringotomy or, better still, preventing the progress of the disease with adequate antibiotic therapy. Happily, otitis media was still the one disease which appeared to react with great regularity to penicillin, and Dr. Hunter had outlined in his practice what appeared to be the ideal treatment for otitis media, and this was the treatment which in general Dr. Simson Hall himself employed in the out-patient department.

In patients not admitted to the ward, a large dose of penicillin was given by injection, say 1,000,000 units, and this was followed by oral penicillin. One of the chief reasons for the widespread use of oral penicillin was the avoidance of repeated visits for the purpose of giving injections where a practitioner was already overworked, but at least one visit was necessary for diagnosis, and therefore a large dose of penicillin could be given on that occasion, and the mother could safely be left to carry on with oral administration. Myringotomy still held its place in certain cases, and the one easily applied test for progress of acute otitis media, and for the necessity or otherwise of this operation, was the testing of hearing. Where the hearing was not seriously reduced intervention was not demanded, but hearing which was deteriorating in face of antibiotics or other administration, demanded further investigation and treatment. In hospital practice one of the most valuable guides was an X-ray picture of the mastoids taken when the patient was first seen, and thereafter this skiagram formed a base-line by which future progress or deterioration could be checked.

Mr. G. H. Bateman (London) stressed the importance of treating the ear as well as the invading organism. He said that in the pre-antibacterial drug age the ear was treated and it was hoped that the body would cope with the organism. There was no way of treating the organism. Now there was a tendency to attack the organism and hope that the ear would look after itself. This was not an acceptable attitude. The ear must still be examined critically and myringotomy performed when there was pus or retained fluid in the middle ear. Inflation was sometimes required to ensure rapid resolution. The treatment of acute otitis media was penicillin systemically and also local treatment to the ear as required by the inflammatory changes in the middle-ear cleft. Only by paying attention to both facets of treatment would the optimum results be obtained.

Mr. Philip Scott (Exeter) strongly advocated the first surgical principle of drainage in otitis media if there was any evidence of fluid within the tympanum and bulging of the drum membrane. General practitioners in one area, near where he lived, frequently called him in to perform myringotomy, and it was his experience that in no such case had it been necessary to open the mastoid; all the mastoid operations which were done were in cases from other areas which had not been so treated and thus drainage had not been established. The first requirement of any treatment for otitis media was to restore normality in the tympanum in the shortest possible time if damaging loss of function was not to follow this condition. He agreed that the early use of intramuscular penicillin in large doses might be an advantage provided fluid had not already caused bulging of the drum, but the early relief of symptoms following the oral administration of antibiotics misled the parents and the doctor into thinking all was well, and there was a great danger that an undrained collection would organize within the tympanum or the mastoid and permanent deafness might result.

Dr. Stuart Carne (London) said there were several different types of acute otitis media—each with its own natural history and its own clinical picture. The drum which showed "ice-floe cracking", for example, cleared rapidly with an adequate dose of intramuscular penicillin; while the drum with a pale pink bulging of the postero-superior quadrant appeared to recover without any specific treatment, but tended to recur. He asked whether the antibiotics had replaced the deafness of suppurative otitis media with the deafness of serous otitis media.

Mr. Otty, in reply to Dr. Carne, said that in his experience antibiotics given in adequate dosage have not increased the incidence of serous otitis media.

Dr. J. I. Munro Black (Newcastle upon Tyne) said the treatment of acute otitis media had been discussed at the annual meeting of the British Medical Association in 1953. It was agreed then that this condition had become the responsibility of the general practitioner. The place of the otologist was to study the failures of treatment to see why they had occurred. One of the reasons for failure had been found to be stopping antibiotic treatment before complete cure. The position would appear to be the same to-day. If there was any criticism to level at the general practitioners it might be that there were some cases being left with residual deafness. There

was no excuse for any doctor offering treatment to a patient with otitis media unless he himself saw the patient again to be sure that cure had occurred before treatment was stopped. It was now suggested that he must also see the patient at a later date to be sure that hearing had returned to normal, and if it did not do so then reference for an otological opinion was required.

REFERENCE

BLACK, J. I. M. (1954) *Newc. med. J.*, **24**, 284.

Mr. Peter Huggill (Taunton) said he supported Mr. Bateman who had reminded them that, while they could treat the infection with antibiotics, they were treating an ear. He was surprised that, although several speakers mentioned myringotomy, there had been so little reference to what he liked to call "the other end of the tube". He believed the eustachian tube to be the key to the middle ear, and that deafness after treatment with antibiotics—or without them—was often due to failure of, or delayed, recovery of the function of the eustachian tube. He used 0·5% ephedrine nasal drops routinely and would like to plead for the use of nasal decongestants in all cases of acute otitis media.

Mr. B. S. Carter (Newcastle, Staffs.) stressed that one must be certain that one is dealing with an acute otitis media, and not an exacerbation of latent chronic disease. He had recently treated 2 cases with a history of a few days and a few weeks otorrhœa respectively, and of no previous ear trouble. Yet at operation cholesteatoma was present, in one case reaching to the mastoid tip.

Mr. Stuart Mawson (London) said that in addition to the points already mentioned as indications for myringotomy, and as guidance for the timing of this operation, it might be helpful to add the anticipation and prevention of spontaneous rupture. Following spontaneous rupture there was always loss of membrane tissue due to the necrosis preceding the rupture. After myringotomy there was no loss of tissue, simply a slit that fell together and healed when the discharge ceased. In the long-term consideration of function it would seem always desirable to prevent spontaneous perforation.

Mr. William McKenzie (London) thought that there should be some hesitation in recommending treatment with antibiotics except in the place where a speaker had gained his experience. Treatment with antibiotics must vary from place to place, and the experience in America, for example, was very different from our own.

He thought too, that some of the speakers had relied on experience gained before the introduction of antibiotics. There was no doubt that the use of antibiotics in otology was still not agreed upon, as this discussion on myringotomy could witness, and no doubt if the subject of discussion had been the indications for mastoidectomy in acute mastoiditis, there would have been a similar difference of opinion.

Finally, there was always the difficulty of deciding whether to admit a child to hospital for treatment of otitis media with antibiotics, and this decision had been made more difficult by the suggestion that a child should not be taken suddenly from its family if it could be avoided, for fear of mental upset.

Mr. H. D. Fairman, Mr. Charles Smith, and **Mr. Brian O'Brien** also took part in the discussion.

Meeting
February 5, 1960

The following papers were read:

Experimental Grafting at the Oval Window.—Dr. B. H. COLMAN.

Otorrhœa Due to a Parotid Fistula.—Mr. S. H. RICHARDS.

Report on an Investigation into the Clearing of the Eustachian Tube in Unconscious Goats Whilst under Increased Atmospheric Pressure.—Surgeon Commander G. S. IRVINE, R.N.

The Significance of Mycotic Infection in the Ætiology of Otitis Externa.—Mr. A. E. W. GREGSON and Dr. C. J. LA TOUCHE.

Physiology of the Endolymph.—Professor F. C. ORMEROD.

Otological Problems in Uganda.—Mr. P. E. ROLAND.

The meeting will be reported in the *Journal of Laryngology*.

Meeting
March 4, 1960

There was a discussion on the **Measurement of Deafness** opened by—Dr. GUNNAR LIDÉN (Gothenburg), Mr. KENNETH MCLAY and Mr. GAVIN LIVINGSTONE.

The following also took part in the discussion: Air Vice-Marshal E. D. D. DICKSON, Wing Commander P. F. KING, Mr. FRANCIS MCGUCKIN, Mr. WILLIAM MCKENZIE, Mr. I. A. TUMARKIN, Mr. R. S. VENTERS and Mr. I. S. YOUNG.

The meeting will be reported in the *Journal of Laryngology*.

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Meeting
January 15, 1960

SYMPOSIUM ON CARRIERS OF PENICILLIN-RESISTANT STAPHYLOCOCCI OUTSIDE HOSPITAL

Dr. N. S. Galbraith (Colindale):

Staphylococcal Infections in General Practice

Infections due to antibiotic-resistant strains of *Staphylococcus aureus* have become a major problem in hospitals. In surgical units wound sepsis may occur in 5 to 10% of cases and the incidence of minor sepsis in maternity units may be as high as 20% (Central Health Services Council, 1959). Furthermore Jeffrey and Sklaroff (1958) have drawn attention to the occurrence of sepsis soon after discharge from hospital. Williams *et al.* (1959) have shown that patients acquire penicillin-resistant strains of *Staph. aureus* in their noses during their stay in hospital, and Hurst (1957) has demonstrated that about half the infants born in hospital are still nasal carriers of penicillin-resistant strains between 6 and 12 months after discharge. Goslings and Büchli (1958) found that spread to other members of the patient's household sometimes occurred.

It is apparent that hospitals are foci of infection of penicillin-resistant strains from which dissemination into the general population takes place. The present investigation was made to determine whether staphylococcal sepsis occurring in general practice can be traced to infection in hospital.

Method.—120 patients who presented with staphylococcal sepsis in general practices in North London were studied. The general practitioners collected swabs of the lesions and anterior nares from consecutive cases of staphylococcal sepsis. When a swab of pus could not be obtained the surface of the lesion was swabbed. Dry cotton-wool swabs on wooden sticks were used and forwarded to the laboratory by post in a bijou bottle of transport medium (Stuart *et al.*, 1954).

From two to seven days after the collection of the specimens the patients were visited and a history of hospital contact, penicillin therapy and previous sepsis was obtained from the patients and all members of the household. Nasal swabs were collected from all the members of the household present at the interview.

The swabs were cultivated on blood agar and the staphylococci isolated were tested for coagulase production with 10% human plasma. Coagulase-positive strains were tested for their sensitivity to antibiotics (Taylor *et al.*, 1958) and were phage-typed by the method described by Anderson and Williams (1956).

Clinical features.—Of the 120 patients, three-quarters lived in Hendon and Finchley and the remainder in Camden Town. They were engaged in many different occupations and lived in varied housing conditions. There were 64 males and 56 females. No one age group predominated.

There were 81 patients (67·5%) with boils, carbuncles or superficial abscesses, 15 (12·5%) with styes, 15 (12·5%) with septic fingers and 9 (7·5%) with skin sepsis. 48% of the lesions were on the head and neck, 24% on the arms and 21% on the trunk and legs; in 7% the site of the lesion was not recorded.

Contact with hospital.—12 (10%) of the 120 patients gave a history of having received in-patient treatment in a hospital within six months prior to the onset of their current staphylococcal lesion.

According to the Registrar-General's Statistical Review for 1955 (Registrar-General, 1959) approximately 3·5% of the population were in hospital during a period of six months. This is less than half the proportion of patients in the present series with staphylococcal sepsis who had been in hospital six months before their lesion developed.

371 household contacts of the patients were also questioned; 6% had been in-patients within the past six months. They thus occupied an intermediate position between the general population and the patients with staphylococcal sepsis.

Penicillin and Terramycin resistance.—Staphylococci were isolated from the lesions of 103 of the 120 patients; 34 (33%) of the strains isolated were penicillin resistant, 19 (18%) were resistant to both penicillin and Terramycin and 3 strains were resistant to Terramycin alone. Of the 19 patients with penicillin- and Terramycin-resistant strains, 9 had been in-patients within six months and 6 had visited hospital in the same period. In 4 cases there was no demonstrable hospital contact.

TABLE I.—STAPHYLOCOCCI ISOLATED FROM PATIENTS' LESIONS
Resistance to antibiotics and epidemic phage types

	Total patients	*Staph. aureus* isolated	Resistant to penicillin	Resistant to Terramycin	Epidemic phage type resistant to penicillin
Group A: In-patients within six months ..	12	11	10 (91)	8 (73)	8 (73)
Group B: Visitors within six months ..	28	22	10 (45)	7 (32)	6 (27)
Group C: No hospital contact	80	70	14 (20)	7 (10)	8 (11)

Percentages are given in brackets.

In Table I the percentages of resistant organisms isolated from the lesions of three groups of patients are compared. Group A are patients who had been in-patients in a hospital within 6 months prior to the onset of their staphylococcal lesion. Group B, patients who had visited hospital one or more times during the preceding 6 months, includes mainly persons attending out-patient clinics or visiting in-patients as well as those attending hospital for any other purpose. Group C are patients with no hospital contact within six months. It is seen that the greater the degree of hospital contact the higher is the proportion of antibiotic-resistant organisms.

Phage-typing.—Williams (1959) showed that certain phage types of *Staph. aureus* were frequently found in epidemics of sepsis in maternity and surgical wards. He listed 11 types that were found to be associated with epidemics on over 20% of the occasions on which they were received for typing. Types 52/52A/80 and 52/80 have been added because of more recent experience. These "epidemic" types associated with hospitals were penicillin resistant and this combination of "epidemic" type and penicillin resistance is another indication of a hospital staphylococcus. Table I shows that the percentage of penicillin-resistant "epidemic" types increases with greater hospital contact.

Previous penicillin therapy.—In Table II the patients have again been divided into the three groups according to their degree of hospital contact and each group has been subdivided according to the previous history of penicillin therapy. The percentage of penicillin-resistant organisms isolated increased considerably with greater hospital contact and only slightly with a history of penicillin therapy.

TABLE II.—PENICILLIN THERAPY
Within six months of the collection of swabs from the lesions

	Penicillin	*Staph. aureus* from patients' lesions: No. of strains	*Staph. aureus* from patients' lesions: No. of penicillin-resistant strains
Group A: In-patients within six months	Penicillin .. 6	6	6 (100)
	No penicillin 6	5	4 (80)
Group B: Visitors within six months	Penicillin .. 8	6	3 (50)
	No penicillin 20	16	7 (44)
Group C: No hospital contact	Penicillin .. 10	8	2 (25)
	No penicillin 70	62	12 (19)

Percentages are given in brackets.

Nasal carrier rate of patients.—In 103 patients *Staph. aureus* was isolated from the lesion, and of these 49 (48%) were found to be nasal carriers; 13 (27%) of the strains isolated were penicillin resistant, and in 33 of the 49 patients the strains from nose and lesion were identical. Of 23 patients with lesions on the head and neck who were nasal carriers 20 (87%) had identical strains in nose and lesion. Of 24 patients with lesions elsewhere who were nasal carriers 11 (46%) had identical strains in nose and lesion. In two patients the site of the lesion was not recorded.

Nasal carrier rate of household contacts.—There were 371 household contacts of whom 202 were swabbed and 73 (36%) were found to be nasal carriers. Eight of these nasal carriers had been in-patients within six months, and 7 of them carried penicillin-resistant strains. Of the remaining 65 carriers 14 (22%) carried penicillin-resistant strains.

153 household contacts of the 103 patients from whose lesions staphylococci were isolated were examined and 55 (36%) were found to be nasal carriers. Seventeen (11%) carried the same strain of organism as was isolated from the patient's lesion. In Table III the household contacts of two groups of patients are compared. The first group were patients with penicillin-resistant staphylococci in their lesions. 20% of the household contacts carried the same strain in the nose as was isolated from the patient's lesion. In the second group the organisms isolated from the patient's lesions were penicillin-sensitive and the corresponding nasal carrier rate in the household contacts was 5%.

TABLE III.—NASAL CARRIAGE OF *Staph. aureus* IN HOUSEHOLD CONTACTS
Relationship to strain isolated from patient's lesion

	Household contacts: No. examined	No. carrying *Staph. aureus* in the nose	No. carrying same strain as patient's lesion
Patients with penicillin-resistant staphylococci in lesions	60	20	12 (20)
Patients with penicillin-sensitive staphylococci in lesions	93	30	5 (5)

Percentages are given in brackets.

Discussion

10% of the patients had been in-patients within six months prior to the development of their

staphylococcal lesion compared with an estimated national average figure of 3 to 4%. An intermediate figure of 6% was obtained from the household contacts. This suggests an association between contact with hospital and the development of a staphylococcal lesion. The increasing percentage of antibiotic-resistant strains and "epidemic" types associated with increasing hospital contact confirms this. Taking resistance to penicillin and Terramycin as indicative of a hospital staphylococcus, 19 patients carried a hospital strain. All but 4 of these gave a history of a recent direct contact with hospital. It seems improbable that these 15 patients were more prone to sepsis than the other patients studied. Only 2 of them gave a history of sepsis within twelve months before attending hospital, compared with 52% in the remaining 105 patients.

The figures in Table II are small but suggest that contact with hospital is more important than a history of penicillin-therapy in the acquisition of a penicillin-resistant strain of *Staph. aureus*. This is in agreement with Goslings and Büchli (1958) who state that the pattern of resistance of a colonizing staphylococcus is mainly decided by the pattern of resistance of the strain of staphylococcus circulating at that moment and only partly by the type of antibiotic therapy.

11% of the household contacts examined were nasal carriers of the same strain of *Staph. aureus* as was isolated from the patient's lesion, indicating a spread of infection in the household. Table III shows this spread to be related to the penicillin sensitivity of the organism in the patient's lesion, there being greater spread when the organism was resistant.

Acknowledgments.—I am indebted to Dr. C. E. D. Taylor, Director, Routine Diagnostic Laboratory, Colindale, who examined all the specimens in this survey, to Dr. R. E. O. Williams, Director, Staphylococcus Reference Laboratory, Colindale, who carried out the phage-typing of the strains of *Staph. aureus* isolated, and to the following general practitioners who took part in the field investigation: Drs. R. W. Cockshut, C. I. Cohen, M. J. Gordon, D. B. Hermann, C. M. Hewat, A. Hill, J. M. Hodson, C. Hotson, R. Hunt-Cooke, B. W. Knight, J. F. Lineen, P. M. Lissack, J. W. McCarthy, O. F. T. Smyth, H. Snowden, A. Spier, E. E. Stephens, D. S. Stewart, K. R. Todd and O. I. Todd.

REFERENCES

ANDERSON, E. S., and WILLIAMS, R. E. O. (1956) *J. clin. Path.*, **9**, 94.

Central Health Services Council, Standing Medical Advisory Committee (1959) Staphylococcal Infections in Hospitals: report of the Subcommittee. H.M.S.O., London.

GOSLINGS, W. R. O., and BÜCHLI, K. (1958) *Arch. intern. Med.*, **102**, 691.

HURST, V. (1957) *J. Hyg., Camb.*, **55**, 299, 313.

JEFFREY, J. S., and SKLAROFF, S. A. (1958) *Lancet*, i, 365.

Registrar-General (1959) Statistical Review of England and Wales for the year 1955. Supplement on hospital in-patient statistics. H.M.S.O., London.

STUART, R. D., TOSHACH, S. R., and PATSULA, T. M. (1954) *Canad. J. publ. Hlth.*, **45**, 73.

TAYLOR, C. E. D., HEIMER, G. V., and SPICER, C. C. (1958) *J. clin. Path.*, **11**, 421.

WILLIAMS, R. E. O. (1959) *Lancet*, i, 190.

——, JEVONS, M. P., SHOOTER, R. A., HUNTER, C. J. W., GIRLING, J. A., GRIFFITHS, J. D., and TAYLOR, G. W. (1959) *Brit. med. J.*, ii, 658.

Dr. J. C. McDonald, Dr. D. L. Miller,[1] Dr. M. Patricia Jevons, and **Dr. R. E. O. Williams** (Colindale):

Nasal Carriers of Penicillin-resistant Staphylococci in Recruits to the Royal Air Force

An analysis by the Public Health Laboratory Service (1958), of fatal cases of Asian influenza during the autumn of 1957 showed that staphylococcal pneumonia was probably an important cause of death, and that 35% of the strains isolated from patients not admitted to hospital or dying within forty-eight hours of admission were resistant to penicillin. Most of these patients were clearly not infected in hospital, yet it seemed unlikely that so high a proportion of the staphylococci carried by the general population would be resistant to penicillin. We therefore decided to investigate the carriage of resistant staphylococci in healthy men and some associated factors.

New recruits to the Royal Air Force, coming from all parts of the British Isles, present a reasonably representative sample of the population, though in a narrow age-group. All new recruits were examined immediately on arrival from civilian life during a period in September 1958 and again in April 1959. In addition, the medical officers of recruit units were asked to take swabs from untreated septic lesions during the autumn of 1958 and again in 1959.

Methods

In the first survey in September 1958, 1,858 recruits were seen, mostly within 6 and all within 24 hours of arrival from their homes; 8 declined to take part in the inquiry and the remainder were questioned and swabbed. Each man was asked (1) his home address, (2) the ages of all younger persons living in the same household, and whether any under 2 years of age were born at home or in hospital, (3) whether he or anyone in the household had had a septic skin lesion, or been admitted to hospital since January 1, 1958, and (4) whether he had received penicillin by mouth or injection since January 1, 1958. A nasal swab was taken from each man, using the same swab

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to sample the anterior parts of both nostrils. The swab was spread at once on nutrient agar containing 5% horse serum and 0·01% phenolphthalein phosphate in 9 cm Petri dishes; half a plate was used for each swab. Incubation of the plates at the Staphylococcal Reference Laboratory at Colindale was begun on the same day as the swabs were taken.

In the second survey in April 1959, the procedure was modified in order to reduce the amount of laboratory work. 1,942 recruits were questioned in groups of about 30. All those with an infant under 2 years of age living in the same household, and all those who had been in hospital or had a septic skin lesion, or been given penicillin since August 1, 1958, were asked to come forward; 415 recruits responded. A further 4 men without these characteristics were chosen at random from each group—a total of 290. The 705 men thus selected were then questioned and swabbed in a similar manner to those in the first survey.

Swabs taken from septic lesions untreated with antibiotics in men reporting sick at recruit camps in the autumn of 1958 and 1959 were posted to Colindale in 5-ml bottles containing Stuart's medium (Moffet *et al.*, 1948). A total of 99 swabs was received, 45 in 1958 and 54 in 1959.

All the cultures were incubated at 37° C overnight. Immediately before examination each plate was exposed to ammonia vapour. Colonies that rapidly became deep pink in colour were subcultured to blood agar and tested for coagulase by the slide clumping test; those found negative were retested by the tube method. All coagulase-positive strains of *Staphylococcus aureus* were tested for phage type, using the basic set of phages agreed by the International Committee on Phage Typing of Staphylococci (1959). A paper disc containing 2 units of penicillin was applied to the typing plates. Any strains that appeared penicillin resistant by this test were examined for sensitivity to a range of antibiotics, including penicillin, using impregnated discs on a plate inoculated to give a semi-confluent growth of staphylococci. When the sensitivity to penicillin was in doubt the strains were tested for penicillinase production and only penicillinase-producing strains were regarded as resistant.

In the first group 72 cultures were either unidentified or accidentally destroyed so that only 1,778 of the 1,850 recruits were retained in this survey. In the second survey there were no losses.

Results

The combined nasal carrier rate of *Staphylococcus aureus* in the two surveys was 42%, similar to that in many other studies. Of the strains isolated 14% were resistant to penicillin, the carrier rate of resistant strains thus being 6%.

The proportion of penicillin-resistant strains was considerably higher than average among carriers who came from a household where there was a baby under 2 years of age, or who had a history of recent admission to hospital, a septic lesion, or penicillin treatment (Table I). There were, however, no consistent differences between the total staphylococcal carrier rates of men with these four characteristics and those without any of them. The results of the two surveys were similar and therefore are shown combined in Table I.

TABLE I.—STAPHYLOCOCCAL CARRIER RATES AND PROPORTIONS OF STRAINS RESISTANT TO PENICILLIN IN MEN WITH VARIOUS CHARACTERISTICS (BOTH SURVEYS COMBINED)

	No. of men	Carrier rate		Proportion of strains resistant to penicillin
		All strains	Penicillin-resistant strains	
1. Baby in household under 2 years of age:				
(*a*) Born at home	82	49%	9% } 10%	17% } 21%
(*b*) Born in hospital	189	47%	12%	25%
2. Admitted to hospital within the last nine months	126	33%	8%	24%
3. Septic lesion within the last nine months	248	47%	11%	23%
4. Treated with penicillin within the last nine months	281	36%	8%	24%
Total with any of the above characteristics	757	43%	9%	22%
Total without any of the above characteristics:				
(*a*) Swabbed	1,726	40%	5%	12%
(*b*) Not swabbed	1,237	—	—	—
Total men studied	3,720	42%*	6%*	14%*

*In the second survey, only 290 of the 1,527 men without any of the characteristics 1–4 were swabbed; these rates are therefore estimated on the assumption that results obtained on this sample were true of the 1,237 not swabbed.

Carrier rates were not closely related to the number of younger persons in the household. Admission to hospital or sepsis in other members of the households did not affect carrier or resistance rates.

It is often suggested that penicillin-resistant staphylococci spread mainly from hospitals, and it is known that epidemics in hospitals are associated with resistant strains which frequently belong to one of a relatively small number of phage types. A selected group of "hospital" types, including those from epidemics in maternity, surgical or general hospital wards between 1954 and 1957 (Williams, 1959) and types 52/52A/80 and 52/80 prominent in more recent epidemics

TABLE II.—PROPORTION OF STRAINS BELONGING TO SELECTED "HOSPITAL" PHAGE TYPES (BOTH SURVEYS COMBINED)

Recruit characteristics	All strains		Penicillin-resistant strains	
	No.	Selected hospital types (%)	No.	Selected hospital types (%)
1. Baby in household under 2 years of age:				
(a) Born at home	40	17%	7	14%
(b) Born in hospital	89	17%	22	27%
2. Admitted to hospital within last nine months	42	31%	10	60%
3. Septic lesion within last nine months	116	18%	27	37%
4. Treated with penicillin within last nine months	97	22%	23	43%
Total with any of the above characteristics	322	20%	70	34%
Total without any of the above characteristics	682	20%	82	38%

were therefore looked for. The proportion of strains belonging to these selected hospital phage types in men with different characteristics is shown in Table II. Of the four characteristics, only a history of recent admission to hospital was associated with an excess of the hospital types. There was no excess of maternity hospital or Group I types carried by men with a hospital-born baby in the household.

Strains belonging to the selected hospital phage types were more often resistant than strains of other types. This was true of strains carried both by men with any of the four characteristics in whom 37% of hospital types were resistant compared with 18% of other types, and by those without the characteristics in whom 22% of hospital types were resistant compared with 9% of other types.

Carrier and resistance rates were calculated for recruits coming from the various geographical regions of the British Isles (Table III). Only the results for the first survey were used since comparable figures for the second survey were not available. Apart from a low carrier rate (31%) with a low proportion of penicillin-resistant strains (9%) in the Eastern and North Midland Regions, and a high proportion of resistant strains (26%) in the South and South-West, there was little variation. When a similar analysis was made for recruits coming from urban and rural areas, it was found that those from rural districts carried a higher proportion of penicillin-resistant strains than those from boroughs and urban districts. This unexpected result was found in both surveys and was true for men with and without the characteristics associated with a high rate of resistance in Table I (Table IV). The difference could not therefore be attributed to an undue frequency of these characteristics in men from rural areas.

TABLE III.—CARRIER AND RESISTANCE RATES RELATED TO LOCATION OF HOME ADDRESS (FIRST SURVEY ONLY)

Location of home address	No. of men	Carrier rate	Proportion of strains resistant to penicillin
North of England, East and West Ridings (I and II)*	249	44%	15%
East and North Midlands (III and IV)*	254	31%	9%
London and South-East (V)*	420	38%	14%
South and South-West (VI and VII)*	191	41%	26%
Wales and Midlands (VIII and IX)*	229	41%	12%
North-West (X)*	213	47%	13%
Scotland and Ireland	222	40%	17%
Total	1,778	40%	15%

*Registrar-General's Standard Regions.

Of the 88 staphylococcal strains isolated from 99 septic lesions among recruits during their first two months of service, 26 (30%) were resistant to penicillin and 25 (28%) belonged to the selected hospital phage types, compared with 14% and 20% respectively for nasal strains. Fourteen (54%) of the 26 penicillin-resistant strains were of epidemic types.

Discussion

Our surveys show that in the general population there has been no increase in the proportion of penicillin-resistant staphylococci comparable to that seen in hospitals. Only 6% of the men we studied were carrying resistant strains and it is quite possible that even before the discovery of penicillin there were some carriers of resistant organisms. On the other hand 30% of strains isolated from lesions were resistant to penicillin, which is similar to the 35% in fatal cases of influenza (Public Health Laboratory Service, 1958) and more than double the figure (14%) in nasal carriers.

The high proportion of penicillin-resistant staphylococci carried by men with a history of recent admission to hospital or contact with a

TABLE IV.—CARRIER AND RESISTANCE RATES IN MEN FROM URBAN AND RURAL AREAS

	Men with specified characteristics*			Men without specified characteristics*		
	No.	Carrier rate	Proportion penicillin-resistant	No.	Carrier rate	Proportion penicillin-resistant
County boroughs and urban districts	628	43%	21%	1,449	40%	11%
Rural districts	129	40%	29%	277	35%	17%

*1 to 4 in Table I.

baby born in hospital could reasonably be attributed to direct or indirect acquisition of staphylococci from hospital. Supporting evidence from phage type distribution was found in recruits who had recently been admitted to hospital but not in those in contact with a baby born in hospital. There was also little evidence from phage type analysis that men with a recent history of a lesion or of penicillin treatment, who also carried a high proportion of resistant staphylococci, acquired many of their organisms from hospitals. It is possible, however, that the "hospital" phage types selected, though associated with hospital epidemics, do not fully represent the range of strains spread from hospitals—particularly those from maternity units.

Of the men treated with penicillin 69% received it for diseases other than septic lesions. The high rate of penicillin resistance in their nasal staphylococci therefore probably resulted from either the survival of, or reinfection with, resistant organisms. The high proportion of resistant staphylococci found in the noses of men with a recent history of a lesion probably reflects the high resistance rate in strains recovered from lesions. This high rate supports the idea of an association between resistance and virulence but no evidence was found that this association was inherent rather than due to selection, since strains of the same phage types varied in resistance.

The veterinary use of penicillin and the consumption of unpasteurized milk, which may contain resistant staphylococci (Tee, 1957) and small quantities of penicillin (Panes *et al.*, 1957), may account for the higher rate of resistant strains found in recruits from rural areas.

Acknowledgments.—We are indebted to Air Commodore J. S. Wilson, formerly Director of Hygiene and Research, Royal Air Force, and to Group Captain J. Roche, Senior Medical Officer, Royal Air Force, Cardington, for their help with this investigation, and to the Director-General of the Royal Air Force Medical Services for permission to publish this report.

REFERENCES

International Committee on Phage Typing of Staphylococci (1959) *Int. Bull. Bact. Taxonomy & Nomenclature*, **9**, 115.

Moffet, M., Young, J. L., and Stuart, R. D. (1948) *Brit. med. J.*, ii, 421.

Panes, J. J., Edge, M., Hobson, M., and Thomas, S. B. (1957) *J. Soc. Dairy Tech.*, **10**, 81.

Public Health Laboratory Service (1958) *Brit. med. J.*, i, 915.

Tee, G. H. (1957) *Mon. Bull. Minist. Hlth Lab. Serv.*, **16**, 141.

Williams, R. E. O. (1959) *Lancet*, i, 190.

Dr. J. A. Rycroft (Southend) and **Dr. R. E. O. Williams** (Colindale):

Penicillin-resistant Staphylococci in Normal Young Children

A great number of studies in the past few years have shown that practically all babies born in hospital become nasal carriers of *Staphylococcus aureus* within the first two weeks of life. Most of them acquire their staphylococci from the hospital environment and so must commonly acquire penicillin-resistant strains. Hurst (1957) showed that some babies retain the staphylococci for many months after they leave the maternity hospital and that among normal children in California the frequency of carriers of penicillin-resistant strains was greatest in the youngest children, and decreased with increasing age (Hurst, 1958). This suggested that the penicillin-resistant strains carried by children might commonly be derived from the hospitals in which they were born.

We have studied the frequency of carriers of penicillin-resistant staphylococci among normal children under 5 years of age living in the County Borough of Southend-on-Sea. Our results are very similar to those of Hurst in California.

Material and Methods

With the help of Dr. W. C. Cockburn and Dr. J. S. Logan, the Medical Officer of Health of Southend, successive stratified random samples of children were drawn from the Health Department birth registers to provide approximately 1,000 children, with equal numbers in each year of life between 0 and 5, and equal numbers born in hospital and at home. Children for whom there were no records in the Health Visitors' files were excluded. Letters were sent to the parents of the selected children and a visit was made to the house by a nurse. Nose and throat swabs were taken from the children, using moist cotton wool swabs, and a brief questionnaire was completed. Of the 2,135 children selected from the registers 1,095 were rejected for various reasons of health, no record, home conditions, &c. 1,040 were satisfactorily examined.

The swabs were returned to the laboratory and plated on blood agar within three to six hours of collection. The plates were examined after incubation at 37° C overnight and again after a further twenty-four hours on the bench. Any coagulase-positive strains (referred to as *Staphylococcus aureus* or simply staphylococcus) were subcultured and tested for sensitivity to penicillin on a 2-unit penicillin ditch plate. Strains resistant to penicillin were further tested for sensitivity to tetracycline, streptomycin, chloramphenicol and erythromycin by means of Sentest tablets. All coagulase-positive staphylococci were tested for phage type at the Staphylococcus

Reference Laboratory, Colindale, employing the basic set of phages recommended by the International Committee on Phage Typing of Staphylococci (1959).

Results

Of the 1,040 children 364 were found to have *Staphylococcus aureus* in the nose or throat or both (Table I). Throat carriage, which was relatively frequent in the first year of life, became less frequent later, while nose carriage became commoner. For the remaining analyses in this paper the results from nose and throat swabs have been taken together.

TABLE I.—NOSE AND THROAT CARRIAGE OF *Staph. aureus*

Age (years)	No. of children examined	No. carrying *Staph. aureus*	% of carriers with *Staph. aureus* in—	
			Throat	Nose
0	102	47	60	55
½–	117	28	50	57
1–	441	116	41	65
3–5	380	173	15	88

Altogether 9·6% of the children carried penicillin-resistant staphylococci, and 0·8% carried tetracycline-resistant strains.

Age and place of birth.—The total staphylococcus carrier rate fell sharply in the first year of life and was lowest between about 6 months and 2 years; it subsequently rose and by the third or fourth year it was as high as is commonly found in adults (Table II).

TABLE II.—CARRIER RATES AT DIFFERENT AGES

Age (years)	Children born at—					
	Home			Hospital		
	No.	% carrying *Staph. aureus*		No.	% carrying *Staph. aureus*	
		Total	Penicillin-resistant		Total	Penicillin-resistant
0–	45	42	9	57	49	33
½–	52	27	8	65	22	12
1–	106	25	9	111	23	10
2–	117	21	5	107	36	7
3–	85	34	5	103	50	14
4–5	109	51	10	83	45	7
Total	514	33	7	526	37	12

There was a striking excess of carriers of penicillin-resistant staphylococci among the hospital-born children less than 6 months old. The excess persisted, although much reduced, through all the age groups except the last. It seems most reasonable to attribute this difference to the acquisition of resistant strains in the maternity hospital by the hospital-born children, but there are several other factors that need to be examined.

History of sepsis and antibiotic treatment.—At the time of swabbing we inquired whether the child had had any septic lesion within the past month and whether he or she was known to have had antibiotic treatment for this or any other condition during the past year. Penicillin-resistant staphylococci were more common in children who had a history of either sepsis or antibiotic treatment, or both, than in those who had neither (Table III). Within the first three groups the history of sepsis was associated with the highest carrier rate for resistant strains, though this derives from the higher total carrier rates in these children: the proportion of the carried staphylococci that were resistant to penicillin was substantially the same in all of them. These differences could not have been responsible for the difference between the home- and hospital-born children (Table II) because such histories were in fact slightly more common among the home-born —19% compared with 14%.

TABLE III.—HISTORY OF SEPSIS

Child's experience of sepsis and antibiotic therapy	No. of children	Percentage of children carrying *Staph. aureus*	
		Total	Penicillin-resistant
Sepsis and antibiotic ..	40	40	18
Sepsis, no antibiotic ..	39	59	26
Antibiotic, no sepsis ..	92	24	10
Subtotal	171	36	15
Neither sepsis nor antibiotic	851	36	9
Total*	1,022	36	10

*History of 18 not known.

NOTE.—97/502 home-born children, and 74/520 hospital-born children had a history of sepsis and/or antibiotic treatment.

Contact with hospital.—There was no appreciable difference between the home- and hospital-born children in the frequency with which they had been in hospital during the year before the survey, or in the number who came from households of which some other member had been in hospital; and in fact the carrier rate for penicillin-resistant staphylococci was slightly lower in children with a history of hospital contact (7%) than in those with no such history (11%); the proportions of the carried staphylococci that were resistant were 21% and 32% respectively.

Other children in the family.—At the time of swabbing 213 of the children were the only children in their household and 827 lived in households with other children; 39% of the former and 34% of the latter carried *Staph. aureus* and the proportions carrying staphylococci that were resistant to penicillin were 16% and 8% respectively (Table IV). However, the lowest frequency of resistant staphylococci (3%) was among the only children, born at home; the higher total rate for the only children derived from the fact that 72% of them had been born in hospital, compared with 45% of the not-only children. Among those born in hospital, however, the only children had the higher carrier rate; we have no explanation for this difference, which was not confined to the youngest children. In any case, the major difference between the hospital- and home-born children cannot be explained by the differences in numbers of children in the household.

TABLE IV.—EFFECT OF OTHER CHILDREN IN HOUSEHOLD

Age (years)	Place of birth	Only children: No.	Only children: % with *Staph. aureus*: Total	Only children: % with *Staph. aureus*: Penicillin-resistant	Not only children: No.	Not only children: % with *Staph. aureus*: Total	Not only children: % with *Staph. aureus*: Penicillin resistant
Under 1	Home	20	40	10	77	33	8
	Hospital	61	39	26	61	30	18
1–5	Home	39	33	3	378	33	8
	Hospital	93	41	16	311	37	7
All ages	Home	59	36	5	455	33	8
	Hospital	154	40	20	372	36	9
	Total	213	39	16	827	34	8

Phage types of staphylococci.—6 of the 20 children who had staphylococci in both nose and throat had different strains in the two sites; in no case was one strain penicillin sensitive and the other resistant. The distribution over the main phage groups and some of the more important types is summarized in Table V. The similarity

TABLE V.—PHAGE TYPING RESULTS

Phage patterns	Percentage distribution in "phage groups" of staphylococci from children born—: At home: S*	At home: R	In hospital: S	In hospital: R
Group I	29	31	25	45
" II	30	27	29	13
" III	15	8	10	27
" IV, Mixed and unclassifiable	12	10	22	3
Untypable	14	23	15	13
"Hospitalepidemictypes"†	17	39	15	54

*S = penicillin-sensitive; R = penicillin-resistant.
† = the "hospital epidemic types" were taken as: 52A, 79, 52A/79, 80, 52/52A/80, 52/80, 71, 6/7/47/53/54/75 &c., 6/47/53/75 &c., and 77 [based on Williams (1959) and more recent unpublished analyses].

of the distributions for the penicillin-sensitive strains, and for the penicillin-resistant strains from the home-children is notable; in contrast the penicillin-resistant strains from the hospital-children had a rather higher proportion of Group I and III and a lower proportion of Group II and miscellaneous strains. Phage type 80 was very rare and antibiotic-resistant strains of this type (such as have caused epidemics in recent years) were only found in 3 children. The commonest individual patterns were 52A/79 (20 children), 3C/55/71 (18) and 55/71 (16).

Discussion

The most striking feature of our results is the high carrier rate for penicillin-resistant staphylococci among the children under 6 months of age who had been born in hospital, but it is also interesting that, at all ages below 4 years, children who had been born in hospital were rather more often carriers of resistant strains than children born at home. Neither experience of antibiotic treatment nor differences in family structure seem to explain the higher carrier rate for resistant strains in the hospital children and it seems reasonable to conclude that the high rate is in fact due to acquisition of "hospital" staphylococci, and their retention in a few of the carriers for some years. The decline in carrier rate for resistant strains with age probably reflects the loss of some of the staphylococci acquired soon after birth and their replacement by sensitive strains from carriers in the general population. It is, however, possible that the decline represents a change in the prevalence of penicillin-resistant staphylococci in the hospitals, for it has to be remembered that the 4-year-old children were born in hospital four years ago and it might be that at that time newborn infants were less frequently colonized with penicillin-resistant strains than they are now. The steepness of the decline in the carrier rate for resistant strains, however, does not make this explanation seem the most likely.

Our results conform well with those reported by Hurst and they serve to draw attention once more to the part that hospital infection may play in seeding the population with antibiotic resistant staphylococci. They are interesting in the light of the observations of McDonald *et al.* (1960), that recruits entering the Royal Air Force from households containing a hospital-born baby under 2 years of age had a substantially higher carrier rate for resistant strains than the average. In contrast to the R.A.F. survey we could not, at Southend, show any effect from recent contact with hospital.

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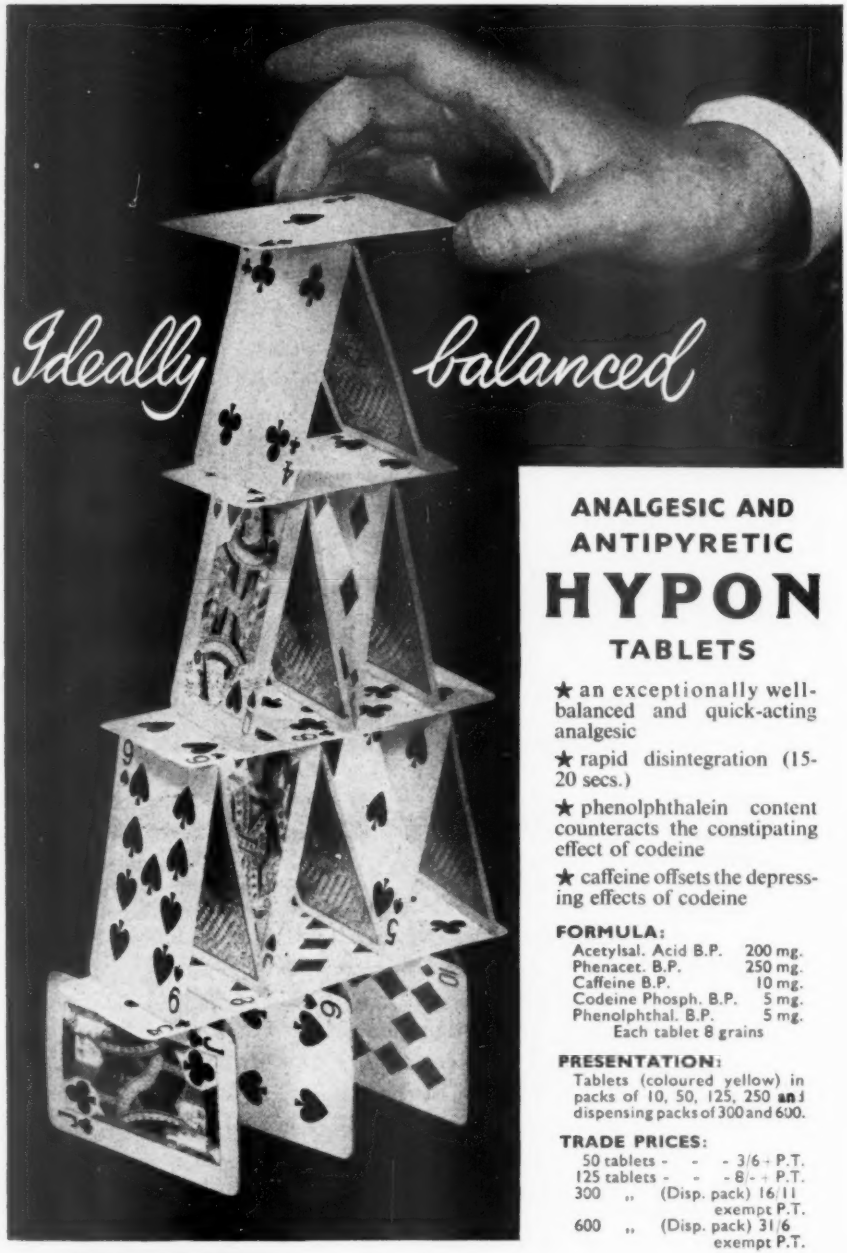
REFERENCES

HURST, V. (1957) *J. Hyg., Camb.*, **55**, 299.
—— (1958) *J. Lab. clin. Med.*, **52**, 254.
International Committee on Phage Typing of Staphylococci (1959) *Int. Bull Bact. Taxonomy & Nomenclature*, **9**, 115.
MCDONALD, J. C., MILLER, D. M., JEVONS, M. P., and WILLIAMS, R. E. O. (1960) *Proc. R. Soc. Med.*, **53**, 255.
WILLIAMS, R. E. O. (1959) *Lancet*, i, 190.



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Section of Neurology

President—DENIS BRINTON, D.M., F.R.C.P.

Meeting
October 1, 1959

The Development of Neurological Services Under the Ministry of Health [*Abstract*]

PRESIDENT'S ADDRESS

By DENIS BRINTON, D.M., F.R.C.P.

London

IN 1945, the committee on neurology of the Royal College of Physicians estimated that the practising neurologists in the United Kingdom and Northern Ireland numbered approximately 60 and that, even with full expansion under the proposed health-service, consultants in neurology would probably never exceed 200 (Royal College of Physicians of London, 1945). The Committee's second report (Royal College of Physicians of London, 1954) stated that the number of neurologists in England and Wales was between 50 and 60 and that more than half worked in London. Table I shows the situation in 1959 for the teaching and non-teaching hospitals of London and of the provinces of England and Wales, and allows comparison with the numbers in 1939. Fig. 1 and Table II illustrate the present geographical distribution of neurologists, with the population in millions which corresponds to one consultant, region by region, except for the metropolitan area which is treated as a whole. They add comparable data for neurosurgeons. The variation in regional ratios is wide. Certain neurologists, notably those practising from Exeter, in the Wessex region, at Preston, and at Derby, are out of contact with any teaching centres. Others, not shown, are similarly situated in the outskirts of the metropolitan regions. Many of these peripheral neurologists are each solely responsible for a number of clinics which may be widely separated. Work in these must therefore stop when the consultant is ill or on leave. All these men are inadequately supplied with junior medical assistants. Some (Exeter, Wessex, and Cambridge) do not have any worthwhile contact with their neurosurgeons. One (Preston) has not yet been allotted any beds although he is in charge of a busy out-patient clinic.

TABLE I.—ESTABLISHED NEUROLOGISTS, 1959
(1939 figures in brackets)

	Metropolitan	Provincial
Teaching hospitals:		
Undergraduate	22 (16)	17 (6)
Postgraduate	5 (3)	—
Regional board hospitals ..	13	10
Totals	40 (19)	27 (6)

The rate of growth of two fairly recently

TABLE II

	Population (millions)	Neurologists	Population per neurologist	Neurosurgeons	Population per neurosurgeon
Metropolitan ..	15·0	40	0·4	19	0·8
Provincial ..	31·4	27	1·2	30	1·1
1. Newcastle ..	2·9	2	1·5	4	0·7
2. Leeds ..	3·0	3	1·0	2	1·5
3. Sheffield ..	4·3	3	1·4	4	1·1
4. E. Anglia ..	1·5	1	1·5	—	—
5. Oxford ..	1·5	3	0·5	2	0·8
10. S. Western ..	2·8	3	0·9	3	0·9
11. Welsh ..	2·6	2	1·3	2	1·3
12. Birmingham	4·6	4	1·2	5	0·9
13. Manchester	4·4	4	1·1	5	0·9
14. Liverpool ..	2·1	—	—	3	0·7
15. Wessex ..	1·7	2	0·9	—	—

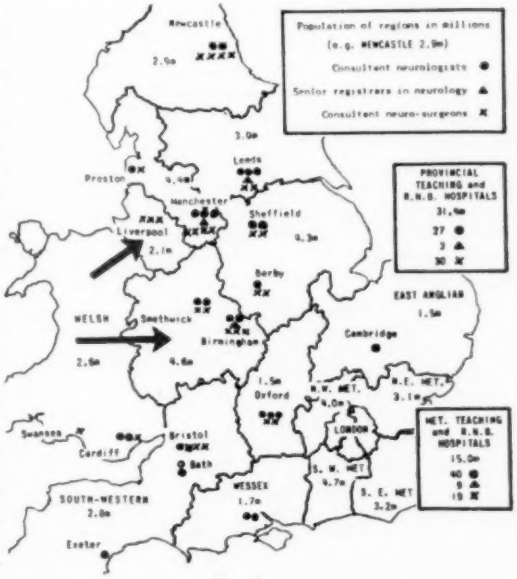

FIG. 1.

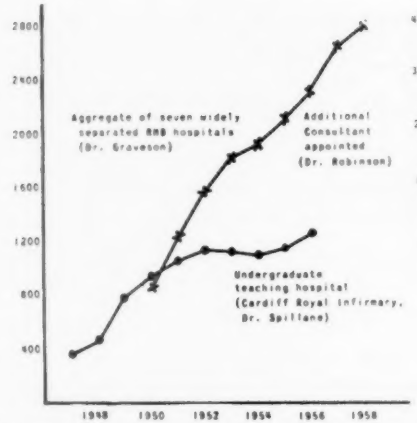

FIG. 2.—New patients at newly established neurological out-patient clinics.

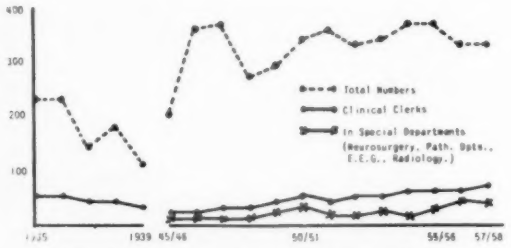

FIG. 3.—Numbers of postgraduate students at the National Hospital, Queen Square, London.

established neurological services is shown in Fig. 2. One is a single clinic at a teaching hospital, which necessarily places a limit on its expansion. The other is a service which consists of seven widely separated clinics, all administered by the Wessex regional hospital board. The establishment of a neurological service quickly demonstrates the needs of the local population.

Most of the consultants in neurology appointed since the war are on a maximum part-time contract. Every neurologist practising to-day would find it difficult or impossible to take on additional sessions. But there are two new burdens which should have long since been shouldered by neurologists. The first is the medical care of epileptics as recommended in the Cohen Report (Central Health Services Council, 1956). The second is the proper supervision of the neurological chronic sick. Boards of governors of teaching hospitals and regional boards have not yet made any serious attempt to implement the recommendations of the Cohen Report, although three years have passed since the appropriate pamphlet was circulated. They may well have felt themselves unable to place any further work on their present neurological consultant staff. The problem of the chronic sick is in a different category; for it has not yet been officially tackled, even by the Ministry. Every practising neurologist is aware of the difficulty of obtaining permanent hospital care for his incurable patients. At the best there is a period of waiting of from six to twelve months. Even when a bed has been obtained, it is often a case of sentencing a relatively young, mentally alert, but paralysed patient to spending the rest of his life in a ward full of old or very old persons, many of whom are more or less demented; nor can a patient so sentenced expect any further specialist treatment, and rarely any physiotherapy or occupational therapy. He is left to rot, physically and spiritually. This situation has lately been the subject of a revealing study undertaken by an almoner, Miss A. Whitaker (1958), with the support of the Nuffield Foundation (unpublished). Between February 1956 and June 1957 she investigated 314 such patients of the North East Metropolitan Regional Hospital Board. All were between the ages of 15 and 55 years. From her diagnostic list, it is evident that 265 (84%) were suffering from organic nervous disease. The size of the whole national problem of the young chronic neurological sick can be roughly gauged from this sample.

The functions of the special hospital in the neurological services of the nation have been recently reviewed by Brain (1958) and Miller (1958). It is again mentioned here only because of the current criticism that British neurology in general and the National Hospital (Institute of Neurology) in particular are tending to drift away from general medicine. Some physicians have even given their opinion that the day of the special hospital is ended. As a place of reference for the difficult clinical problem, as a school for part of the training of doctors who have an interest in neurology, as an institute of research, and as a national or even an international headquarters for all neurologists, there cannot be any substitute for the special hospital. Fig. 3 illustrates the recent progress of some part of the training programme at the Institute of Neurology.

With the increasing complexity of the medical sciences, it is inconceivable that any of these functions could be efficiently discharged by general physicians or by scattered neurologists, each with his own small department in a general teaching hospital. Nearly all the part-time consultants at the National Hospital also work in the general hospitals of the undergraduate medical schools of the University of London. Not one of the staff of the Institute need be out of touch with general medicine.

General physicians with an interest and some special training in neurology are unquestionably useful in a few parts of the periphery of England and Wales in covering the present serious shortage of neurologists; but, if they are to fill even this role, it is essential that they maintain close contact with the nearest neurological centre.

REFERENCES

BRAIN, R. (1958) *Brit. med. J.*, i, 355.

Central Health Services Council (1956) Report of the Subcommittee on the Medical Care of Epileptics. (Cohen Report). London.

MILLER, H. (1958) *Brit. med. J.*, i, 477.

Royal College of Physicians of London (1945) Report of the Committee on Neurology. London.

—— (1954) Interim Report of the Committee on Neurology. London.

WHITAKER, A. (1958) Unpublished report (Nuffield Foundation).

Meeting
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THE PARALYSED BLADDER

The Residual Urine in Bladder Rehabilitation

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GOOD management of the paraplegic requires attention to detail, and there is no short cut to successful rehabilitation. This remark applies particularly to the care of the paralysed bladder and it is important to pay attention to some simple observations before attempting to establish any complicated routine. Although opinion regarding details may vary, the usual practice in the early management of the paralysed bladder comprises some sort of indwelling catheter with trial periods without a catheter until voiding occurs. The management following the first voiding requires patience, experience and an appreciation of the significance of residual urine, which is the aspect to be considered in this paper.

According to Gray's Anatomy the bladder, when distended, assumes an ovoid form, the long diameter being directed upward and forward. Thus the bladder would appear to be something like a funnel in which sediment collects at the apex and is discharged first on release. This happens even in the paraplegic patient when he is erect. This description of the bladder would also suggest that even with the subject supine there would still be a tendency for dense matter to settle in the region of the bladder-neck and to be discharged. Whether this is so in normal subjects I do not know, but it is certainly not so in paraplegics.

It soon becomes obvious that an open catheter fails to empty the bladder and nearly always more urine can be obtained by aspiration after a catheter has finished draining passively. Residual urine is usually defined as the urine obtained by catheterization after voiding, but estimates of the residual urine in the paralysed bladder are useless unless aspiration has been done.

While the paraplegic patient is in bed and has an indwelling catheter it is a most difficult matter to keep the urine free from infection although a strict routine has been followed. On the other hand when a patient is able to sit in a chair and to stand from time to time there is little trouble with urinary infection even though the patient may be draining his own catheter with little regard to hygiene and asepsis. Partially ambulant patients with or without catheters frequently state that when they stand and micturate the first part of the urine voided appears thick. This is in sharp contrast to the experience of catheterizing patients confined to bed when it is the last portion of urine aspirated which tends to contain sediment. This can be very obvious, the first ten ounces or so which are aspirated being quite clear and then suddenly the last half to one ounce being thick and perhaps purulent. It is easy to miss this thick urine when the patient is in bed. On several occasions a routine catheterization has been done, clear urine obtained and the bladder apparently emptied. For some reason the catheter may have been renewed in an hour or less and on this occasion a small quantity of foul, thick, cloudy urine obtained in the last part of the specimen. Such an experience indicates that the relatively dense urine containing deposit may be out of reach of the catheter in the patient in bed and it is largely a matter of chance whether or not this portion of the bladder contents is removed even by aspiration.

In an attempt to explain these clinical observations a series of radiographs was taken using contrast media. The shape of the bladder could be shown by filling it with a 10% solution of sodium iodide, but more than this was required. To demonstrate the drainage of the harmful, infected, heavy deposits in the bladder, Myodil was used. To demonstrate the position of the catheter the bulb of a Foley catheter was filled either with Myodil or with air.

Fig. 1 shows the bladder containing sodium iodide and a small volume of Myodil. The patient is supine and it is clear that almost half

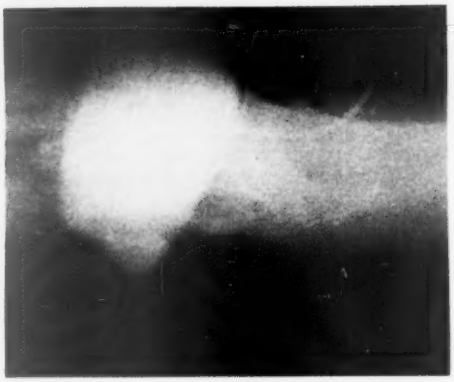


FIG. 1.—Radiograph of the bladder containing sodium iodide and a small volume of Myodil. The patient is supine.

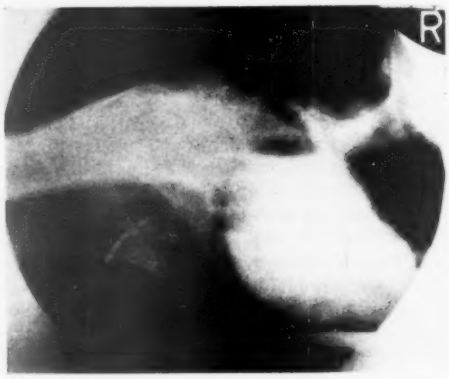


FIG. 2.—Radiograph of the bladder containing sodium iodide with the patient prone. There is air in the balloon, and Myodil in the lumen of the catheter.

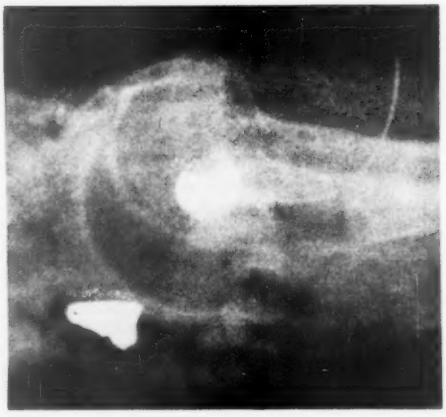


FIG. 3.—Radiograph showing the retention of Myodil in the bladder after passive drainage through the catheter with the patient supine.

FIG. 4.—Radiograph of the bladder showing only a small quantity of Myodil remaining in the bladder after passive drainage with the patient erect.

FIG. 5.—Radiograph of the bladder with the patient supine. Myodil is being injected through a catheter.

FIG. 6.—Radiograph with the patient erect demonstrating that heavy material will readily drain in this posture.

the urine in the bladder is well below the catheter; the heavy material in particular would be unlikely to drain. Fig. 2 is a similar radiograph with air in the balloon of the catheter, some Myodil in the lumen of the catheter; the position of the relatively heavy material is shown with the patient prone. This heavy material is not easily removed from the bladder. Fig. 3 shows the state after passive drainage through a catheter and Fig. 4 shows satisfactory emptying after the bladder has been drained with the patient erect. Figs. 5 and 6 demonstrate in a striking way not only the position of the catheter in the bladder but its relationship to dense material with the subject supine and erect. These radiographs show quite conclusively the effect of the erect posture on bladder drainage. They confirm the unsatisfactory emptying of the bladder when the patient is prone or supine, and show how pockets of foul, thick, urine may remain undisturbed and out of reach of the catheter, and lead to chronic urinary infection and predispose to the formation of stones.

Although in the rehabilitation of paraplegics much attention is paid to the volume of residual urine compared with the volume of urine voided, it may be difficult to say why the quantity of residual urine should be so important. Every now and again patients with old, kyphotic lesions of the dorsal spine or with cauda equina lesions are found to have large bladders but no urinary symptoms. Perhaps these patients escape serious urinary complications because they are ambulant, and pass heavy sediment which might be infected; although there may be a large volume of urine in the bladder, the most harmful part of it drains away. Activity of the patient would therefore seem to be more important in the prevention of urinary complications than the mere volume of residual urine.

Although a paraplegic may survive in reasonable health for many years with a high residual urine, this state of affairs should not be the aim of bladder rehabilitation. Apart from the risks of infection and stone-formation the volume of residual urine is of importance because stretching of the bladder inhibits contraction in the muscle. This may be seen to occur in a bladder which has started to void but where a catheter is still necessary. If the bladder becomes distended, voiding stops subsequently for some time. Similarly in patients with partial recovery of bladder function, distension will sometimes stop further voiding. It is essential, therefore, that in the management of the paralysed bladder distension should be avoided. Care must therefore be maintained in the paraplegic to see that the catheter continues to drip urine, that the association of facial sweating with bladder distension be realized and that the patiten should be trained to take note of the vague and sometimes bizarre symptoms which indicate bladder fullness. When bladder distension is observed, catheterization must not be delayed.

The periods of trial without a catheter must be properly conducted so as to avoid bladder distension, and to secure accurate figures. There is a tendency for these periods of trial to be prolonged, even up to eight hours. If a patient has been drinking large quantities of fluid, overdistension of the bladder may occur in under two hours. Should the trial period be prolonged and the bladder allowed to accumulate 20 oz or more of urine a setback in bladder rehabilitation may follow. Incidentally, the catheter round will take much longer if the patients have over-full bladders. If those who advocate trial periods of several hours were to pass the catheter themselves, they would perhaps soon change their views. For the sake of accuracy it is essential that the bladder should be empty before the trial period begins, but unless the patient is able to stand, it is practically impossible to achieve this state. Unless the residual urine is assessed immediately after voiding the figure obtained is meaningless, but the patient with a paralysed bladder can rarely void urine at will, even by means of tricks, and catheterization must therefore be timed to the patient's voiding rather than by routine. The patient must be instructed to indicate when he has voided and the catheter should be inserted immediately. Catheterization in this way becomes a source of great inconvenience to the staff, but there is no easy way of avoiding it if the trial period is to be of any significance. Once it has been established that the bladder is able to empty reasonably well, the trial period may be extended and the catheter dispensed with altogether.

The aim of bladder management in the paraplegic should be to produce a bladder which is capable of voiding regularly and well with a set volume of urine; and a patient who is able to interpret bladder symptoms and who can assess fluid intake to anticipate voiding. This is a rare combination and one difficult to achieve. To approach this state, bladder distension must not be allowed to occur either by accidental blocking of a catheter; or by overlong trial periods without a catheter; or by removal of the catheter without accurate measurement of the volume of residual urine. Short of this state the patient will be incontinent of urine and the first concern should be the avoidance of urinary complications.

While the patient is in bed, bladder emptying and removal of sediment is difficult and unreliable, but danger may be minimized by the patient's taking large quantities of fluid by mouth, the bladder contents being aspirated and the

bladder washed out when the catheter is changed. Frequent turning of the patient helps to prevent accumulation of the sediment but disturbs it for only a short time. The final volume of residual urine is of importance but it seems likely that more important still is the regular removal of bladder sediment by early mobilization, preferably with the patient erect.

The Neurogenic Bladder in a General Hospital

By Thomas Moore, M.D., M.S., F.R.C.S.

Manchester

Vesical dysfunction is the most important complication of neurological lesions. Both socially and prognostically the urinary tract is often of more significance than the primary disease. In spite of all modern advances in techniques and in the control of sepsis, urinary complications account for 64% of all deaths in paraplegics (Damanski and Gibbon, 1956). Any improvement in this figure can only be achieved by careful study of all the relative causative factors in many types of case, so that a rational and reliable programme for the care and treatment of the urinary tract can be evolved.

Rarely, if ever, is the bladder literally paralysed. The "paralysed bladder" is one in which there is some dysfunction or defect of physiological nervous control. In normal micturition the detrusor muscle is co-ordinated with the sphincter muscle at the bladder neck and in the urethra so that all the urine in the bladder at that time is expelled. The act is functionally efficient and balanced. Interruption of any of the various and complicated nervous arcs causes incomplete ability to retain or to expel urine in a normal manner. Similar imbalance between the detrusor and the sphincter mechanisms can be a late result of primary obstructive disease of the bladder neck in both sexes, as the hypertrophied detrusor muscle eventually becomes unequal to its task of emptying the bladder completely against the increased resistance at the outlet. This residual urine is the most important and significant indication of vesical imbalance.

Neuro-anatomy

The bladder and posterior urethra in the male and the bladder and the urethra in the female act as one unit, controlled by a motor centre in the 2nd, 3rd and 4th sacral segments of the spinal cord. Afferent stimuli from the mucosæ and muscles of the urethra and bladder and inhibitory and facilitatory impulses from the cerebral cortex and other higher centres control the activity of this spinal centre. Interference with the nerve arcs at various levels results in one of the well-recognized types of neurogenic vesical dysfunction:

(1) Uninhibited neurogenic bladder (interruption of cortico-regulatory fibres).

(2) The spinal or automatic reflex bladder (complete anatomical or functional defect of spinal cord above the level of the motor centre).

(3) Autonomous neurogenic bladder, non-reflex (no connexion of the bladder to the spinal motor centre).

(4) Sensory, atonic or tabetic neurogenic bladder (loss of afferent side of reflex arc).

(5) Motor neurogenic bladder (loss of efferent side of reflex arc).

Many workers, including Denny-Brown and Robertson (1933), Munro (1937), McLellan (1939), Nesbit and Lapides (1948), and Prather (1949), have contributed to our basic understanding of the neurogenic bladder. Each, however, has his own ideas as to the nomenclature and thus various names are used for the same condition often leading to confusion. Bors (1951, 1957) has used rather a different basis of classification. He recognizes those due to lesions above the motor sacral centre, supranuclear (corresponding with the upper motor neuron somatic lesions), and those at or below, nuclear or infranuclear (corresponding with the lower motor neuron somatic lesions). All workers divide their cases into incomplete and complete lesions. In addition, Bors has introduced a functional element, the ability of the bladder to empty properly. In every neurogenic dysfunction there is obviously some bladder inefficiency. Empirically he has taken a 20% of capacity residual urine as compatible with good function in upper motor neuron lesions and a 10% residual urine as compatible with good function in lower motor neuron lesions. If the amount of residual urine is higher than this he then regards the bladder as imbalanced and believes that steps ought to be taken to make it a balanced organ.

Ætiology

My experience has been gained in general hospitals (mostly in the Manchester Royal Infirmary) and consulting private practice. It consists mostly of patients with neurological disease to whom this paper is confined. In addition I have perused the records of patients with many of the common neurological diseases occurring in the Manchester Royal Infirmary in

the years 1950 to 1958 inclusive. The incidence of severe urinary symptoms in most of these is shown in Table I.

TABLE I.—ANALYSIS OF NEUROGENIC CAUSES OF SEVERE BLADDER DYSFUNCTION

Disease	Total	Bladder dysfunction
Demyelination	615	68
Tabes dorsalis	125	18
Other types of neurosyphilis	127	10
Cord compression	—	14
Congenital lesions	23	10
Intrathecal phenol	42	5
Spinal anæsthesia	—	1
Cerebral lesions	—	12
Motor neuron disease	170	5
Anterior poliomyelitis	—	1
Syringomyelia	160	1
Subacute combined degeneration of the cord	76	4
Parkinsonism	—	6
Post-rectosigmoidectomy	—	6

By far the commonest cause is demyelinating disease. It will be seen from Table II how common urinary symptoms are in disseminated sclerosis. All types of urinary symptoms occur and in the majority I have no doubt were caused by vesico-neurogenic disease, usually of the uninhibited neurogenic bladder type. These symptoms lasted from six weeks up to fifteen years but then often disappeared. Tabes and other forms of neurosyphilis are the next most common causes of a neurogenic bladder. Among the cases of tabes admitted to the hospital during the period under review there were 18 with tabetic bladder disorder while amongst all other types of neurosyphilis, which included 3 patients with paraplegia, 10 examples of neurogenic vesical dysfunction were encountered. Syringomyelia and subacute combined degeneration of the cord were very unusual causes.

TABLE II.—DISSEMINATED SCLEROSIS. 604 CASES (MANCHESTER ROYAL INFIRMARY 1950–58)

	No. of cases
Urinary symptoms	254
Frequency, &c.	171
Hesitancy, &c.	75
Incontinence	42
Retention	15

Cerebral lesions can cause urinary symptoms. Occasionally acute vascular cerebral episodes may be complicated by a completely atonic bladder such as occurs in spinal shock. Chronic cerebral degeneration may cause urinary symptoms simulating or adding to those caused by prostatic enlargement. No search of the hospital records of all cases of cerebral catastrophes has been undertaken; those included in this survey have occurred in my own practice. Parkinsonism is another disease often met with in prostatic patients. It is my belief that they do not do so well after prostatectomy as other patients, due I suspect to their nervous disease. In these patients the relaxant Artane may affect involuntary as well as voluntary muscle. When there is some obstruction at the bladder neck this drug may render the balance of the bladder incompetent and retention results. Even with a normal bladder neck, if the continuance of the drug is necessary in Parkinsonism it may be necessary to resect the bladder neck to make a large and easy outlet.

Diagnosis

Whatever the ætiology the complaint is one of inability to hold or to pass urine normally. In both sexes with advancing years pathological changes occur at the bladder neck. Even minimal changes there may cause painless chronic bladder distension. As the obstructive cause is not easily recognizable, primary neurogenic disease can be very closely simulated. In addition, lesions of either type may be complicated by the development of the other. Four types are therefore possible:

(1) Primary neurogenic vesical dysfunction.

(2) Primary obstructive uropathy which may simulate (1) very closely.

(3) Primary neurogenic vesical dysfunction complicated by the development of unrelated obstructive changes at the bladder neck.

(4) Primary obstructive uropathy complicated by the development of unrelated neurogenic vesical lesions.

In attempting to distinguish between these types a careful analysis of the patient's sensations during micturition is necessary. Has he, first, the normal desire to micturate, second, the normal ability to inhibit micturition and, third, the normal ability to initiate micturition? Any complaint of incontinence must be carefully evaluated for this may result from any one of the following causes: Precipitate micturition (uninhibited neurogenic bladder), reflex micturition (automatic bladder), strain incontinence (autonomous bladder), overflow incontinence from chronic retention and passive incontinence due to loss of all the normal sphincter mechanisms. The last is by far the rarest type.

Retention is also a common symptom of neurological vesical disease. Some degree of retention evidenced by residual urine is the common denominator in many of the complications of neurogenic bladder disturbance. The principal cause is increased resistance at the outlet of the bladder, either from muscular hypertrophy or inco-ordination. Sometimes spasticity of the external urethral sphincter muscle is a major factor. The primary aim of treatment is to reduce or abolish this residual urine.

As micturition is basically a spinal reflex, clinical investigations of the activity of the reflex arcs subserving it are essential. Although the cells in the sacral cord concerned with the bladder contraction are not identical with those con-

trolling somatic muscles, both groups lie close together in the 2nd, 3rd and 4th sacral segments of the cord. It is therefore unusual for one to be affected without the other. Clinically, therefore, somatic and autonomic conus activity must be evaluated. The bulbo-cavernous reflex is the test of somatic conus activity. Normally by stimulation of the glans penis or the base of the bladder (by pulling on the Foley catheter) contraction of the external anal sphincter is caused. Similar contraction of the external anal sphincter can be caused by the painful stimulation of the peri-anal skin. If no contraction of the muscle can be felt then electromyographic tracings should be made. Bors (1957) estimates autonomic conus activity in cases of traumatic paraplegia by instilling 2 oz of ice-cold water into the bladder through a catheter. If the autonomic sacrospinal reflex is intact, bladder contraction occurs almost at once and expels the water and the catheter. In my wards this test is also used in the investigation of neurogenic bladders due to disease. Sphinctero-cystometry is the most comprehensive method of demonstrating bladder function. Although sometimes difficult to interpret, it is the one method in common use giving some idea of the physiological state of the bladder and sphincter muscles. This gives information about (1) the tone of the external urethral sphincter, (2) the amount of residual urine, (3) the sensitivity of the bladder to hot and cold, (4) the reaction of the bladder muscle to distension, and (5) the presence of vesical contractions together with the patient's ability to initiate or to inhibit them voluntarily. At the same time the extent that the bladder pressure can be raised by abdominal straining and the bladder capacity may be measured.

From these investigations the presence of a neurogenic bladder and its type can usually be decided. Cystoscopy is carried out, often without anæsthesia, to test the patient's urethral and bladder base sensitivity to pain and to estimate the presence of any obstructive lesions at the bladder neck. Complications such as diverticula and stones are also easily demonstrated by this method. Urethro-cystography is also useful in depicting any change in the bladder outline due to trabeculation or the formation of diverticula. It is particularly useful in demonstrating obstructive shelf formation at the bladder neck and spasticity of the urethral muscle. Electromyography (Petersen and Franksson, 1955) is now being applied to the study of neurogenic bladder disease and in the future may be of some value in the estimation of sphincter function and tone and of detrusor activity. Other techniques, including cineradiography and the electrical flow meter devised by Von Garrelts (1956, 1957) may also come to be very useful in the study of vesical dysfunction. But, in spite of all these special investigations, the essential factor is the amount of residual urine, as it is on this that the future course of the case depends. Examination of the urine is regularly carried out to demonstrate any infection and routine intravenous urography is very useful in studying the function of the upper urinary tract and any pathological changes occurring there.

Complications

Complications confined to the urinary tract are unfortunately common in neurogenic vesical diseases.

Infection.—Urinary sepsis in all its various manifestations is the great danger of neurogenic vesical dysfunction. In the male, spread to the genital tract clinically declaring itself as epididymo-orchitis is not uncommon. The inefficient emptying of the bladder may be associated with some degree of ureteric reflux and then urinary infection rapidly ascends to the upper urinary tract. It is unfortunately still true that the common cause of death in cases of neurogenic vesical dysfunction is infection. I know of two examples, one fatal, in which spontaneous rupture of the neurogenic bladder occurred due to a combination of infection and distension. Stone formation may also occur because of infection and stasis in the bladder and upper urinary tract. Stones in the bladder can be removed transurethrally or by open operation. Renal stones can be similarly treated but in many they are associated with gross infection. In the presence of pyonephrosis, particularly when this is unilateral, radical surgery is the best treatment (Fig. 1A, B).

Fistula formation.—The loss of sensation to pain in these patients allows abnormal pressures to be exerted in various parts of the body with the formation of bedsores. This factor also applies to the urethra. The urethral catheter therefore must be as small as is compatible with adequate drainage. Great care must be taken to avoid prolonged pressure on the urethra between the catheter and any other structure, such as the edge of the mattress or chair. If these points are not carefully attended to urethral fistulæ, usually at the penoscrotal angle, will form and are very difficult to treat.

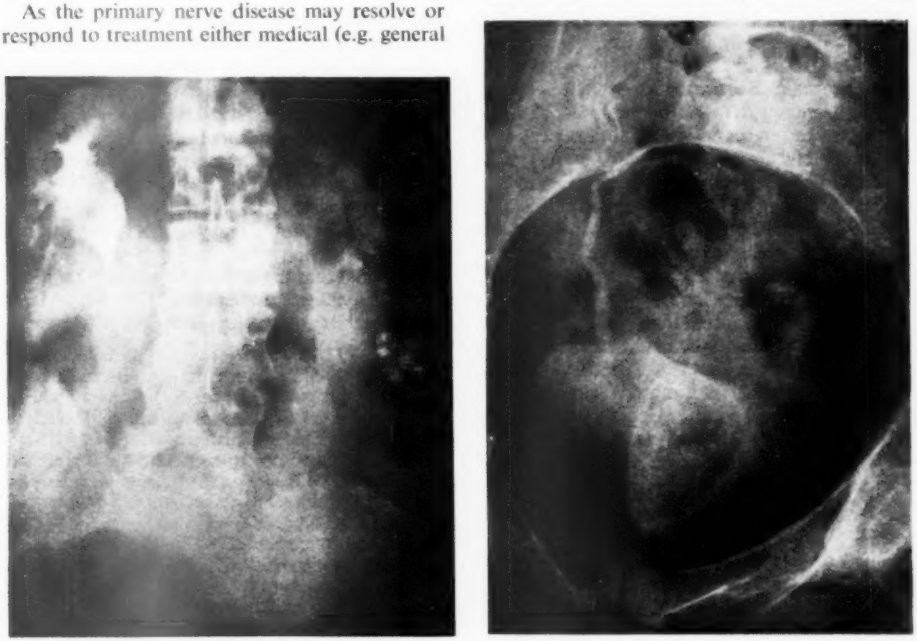
Prognosis of the Urinary Affection

Incomplete lesions usually result in a urinary apparatus over which the patient has some voluntary control. Although treatment may be necessary for various factors sepsis is not usually a great complication and the prognosis is therefore good. Complete lesions leave the patient without the sensation of micturition and with no

voluntary control. In the reflex type of bladder, recovery depends on the bladder capacity and the absence of sepsis. If the bladder empties at intervals of two hours or longer the patient may be able to be continent and live a fairly normal life. In the non-reflex type function depends similarly on the bladder capacity and the ability of the patient to express the bladder contents by suprapubic pressure and abdominal muscle contraction. These of course depend upon the extent to which these structures have been interfered with by the primary nervous disease. Treatment can make the bladder more efficient and improve prognosis if the residual urine is high. If bladder function is well balanced, sepsis can usually be controlled. Damanski and Gibbon (1956) found, however, that in some patients dilatation of the upper renal tract and renal dysfunction tended to increase as the years passed.

Treatment

As the primary nerve disease may resolve or respond to treatment either medical (e.g. general treatment of syphilitic paraplegia and early tabes dorsalis) or surgical (e.g. relief of cord compression) during the early stages the bladder management must be conservative. During this time over-distension and fibrous contraction of the bladder must be prevented. Infection of all kinds must be avoided, stone-formation made unlikely and fistulæ avoided. When retention is present it is necessary to drain the bladder by indwelling catheter. Other methods of surgical drainage, suprapubic cystostomy and perineal urethrostomy are not necessary. The smallest catheter compatible with drainage should be used in the early stages; a Gibbon catheter is quite satisfactory but when there is any gross infection present it easily blocks and a 16 Ch. 5-ml Foley catheter is preferable. To prevent a contracted bladder the catheter must be blocked for two to three hours each day or connected to a tidal drainage apparatus, the height of the siphon of which is controlled cystometrically. Although in my experience efficient tidal drainage has been satisfactory, Lapides (1957) believes that it is the less satisfactory method. The essential watchword during this time is asepsis. The external genitalia should be shaved and the catheter passed with the greatest aseptic precautions and kept clean by regular attention. Free fluid by mouth, at least 6 pints per day, is probably the



A B

FIG. 1A, B.—Female aged 61 years; paraplegia due to disseminated sclerosis with balanced reflex bladder. Recent "incontinence" caused by cystitis with vesical calculus and left calculous pyonephrosis. Intravenous urogram (A) and intravenous cystogram (B) showing stones and loss of function of left kidney and large, partially non-opaque calculus in bladder. Restored to balance by suprapubic cysto-lithotomy and left nephrectomy.

best method of irrigation as there is less chance of contamination. Where sepsis has occurred continuous or intermittent irrigation with one of the new antiseptics such as chlorhexidine (Hibitane) is useful. In my view it is better to keep the urine acid by giving Mandelamine by mouth and to use a safe sulphonamide such as sulphafurazole. If infection with resistant organisms occurs short courses of the necessary antibiotics should be given. If a Gibbon catheter is used and there is no infection it may be left in position up to forty days (Ross, 1956). A Foley catheter should be removed at weekly intervals to test the development of bladder function. Regular cystometry reveals the return of detrusor contractions, which may be encouraged by blocking the catheter for increasing periods of time intermittently during each day. This helps to train the bladder and sphincter muscles. During trial periods without the catheter, giving a reliable muscle stimulant such as carbachol 2 mg six-hourly is very useful.

A point which is often neglected and which is of the very greatest importance from the point of view of asepsis, is attention to the bowel. Persons with neurogenic disease are very prone to develop fæcal impaction with false incontinence. It is not difficult to see how contamination of the catheter is thereby encouraged. In addition a loaded bowel, even apart from neurogenic disease, is a frequent source of urinary difficulty. Many patients with mild urinary symptoms, due either to primary urological disease or secondary neurogenic factors, remark how much better they empty their bladders when the bowel is empty.

When it is considered that the effect of the neurological disease on the bladder has reached a permanent state the problem of future management of the urinary tract must be decided. If there is any residual neurogenic defect micturition will, in some way, be inefficient. As it is not possible to restore the lost innervation all that can be done is to attempt to improve bladder efficiency. The surgical treatment which has been carried out in this series is shown in Tables III, IV and V.

In incomplete supranuclear lesions the uninhibited contractions may be damped down by giving anticholinergic drugs such as Banthine or Pro-Banthine. If excess sensory stimuli from the bladder or pelvic floor muscles appear to be playing a part these may be reduced, sometimes permanently, by trial of temporary vesical mucosal, pudendal, regional or spinal analgesia. In such incomplete lesions there is usually some degree of voluntary control but bladder function may be poor, partly due to local pathology at the bladder neck. This often leads to residual urine which, with the neurogenic precipitancy, is often classified as incontinence. These patients can be helped by removal of the bladder neck obstruction either by transurethral or open operation.

When the spinal motor centre remains completely divorced from higher control and sensation a reflex bladder results. If this has a good capacity it may empty involuntarily at two- to three-hourly intervals with a residual urine of less than 20%. Such a bladder is in as satisfactory a state as possible and infection is controllable. Often, however, this happy state is not realized and the bladder empties frequently and incompletely, sepsis is rife and life intolerable. For these, an attempt to restore the balance by resecting the bladder neck, usually transurethrally, is carried out. In my experience gratifying results have been obtained. If urination still is not sufficiently complete the state of the external sphincter must be investigated. If this is spastic then the effect of pudendal nerve blocks is tried and if successful is followed by bilateral pudendal neurectomy. Such treatment may also give gratifying results. If unsuccessful the spastic external sphincter must be cut away transurethrally leaving the patient completely incontinent so that the urethra is used as a catheter and an efficient rubber urinal fitted. Many people lead useful and happy lives in this state.

Case 1.—T. B., aged 56. Intrathecal dermoid cyst removed 1950. Much trouble afterwards with micturition and marked upper urinary tract involvement complicated by gross infection. An inefficient type of reflex bladder, first treated by suprapubic cystostomy. First seen by me in 1958. Suprapubic cystostomy closed. In an attempt to render the bladder more efficient transurethral resection of bladder neck, bilateral pudendal neurectomy and transurethral resection of external sphincter were successively carried out. The latter procedure made an incredible difference to him. Wearing an efficient rubber urinal he became a normal, cheerful member of society again.

If the final outcome of the disease is a bladder completely freed from all cord impulses (the autonomous or non-reflex bladder) the patient, if

TABLE III.—SURGICAL TREATMENT

	No. of cases
Suprapubic resection of bladder neck	9
Transurethral resection of bladder neck	28
Ileal conduit	2
Ileocæcal bladder	2
Transurethral resection of external sphincter	1
Bilateral pudendal neurectomy	1

TABLE IV.—SUPRAPUBIC RESECTION OF THE BLADDER NECK

	No. of cases
Congenital lesions	2
Disseminated sclerosis	1
Tabes dorsalis	1
Cerebral lesion	1
Post-rectosigmoidectomy	2
Parkinsonism	2

TABLE V.—TRANSURETHRAL RESECTION OF BLADDER NECK

	No. of cases
Disseminated sclerosis	10
Tabes dorsalis	6
Neurosyphilis	2
Motor neuron disease	1
Post-rectosigmoidectomy	4
Parkinsonism	2
Post-intrathecal phenol	2
Cord compression	1

otherwise able, can empty the bladder by manual suprapubic compression and abdominal straining with a residual urine of 10% or less. Such a condition is the most satisfactory state possible in this lesion. Other patients, however, leak small amounts of urine quite involuntarily and usually at very short intervals and then transurethral resection of the bladder neck gives satisfactory results in reducing the residual urine to reasonable proportions and allowing easy manual emptying of the bladder. Although this would hardly be expected, pudendal neurectomy and cutting away the external sphincter have produced improvement in some such patients (Ross, 1956).

In the atonic neurogenic bladder the detrusor muscle becomes stretched by the gradual accumulation of urine because of the loss of the afferent impulses in the bladder wall. Many of these patients may be helped by bladder muscle stimulants (carbachol) or by training the patient to empty his bladder by the clock using abdominal straining and manual suprapubic compression. If this is not sufficient to reduce the residual urine, transurethral resection can give good results. The basis of this procedure is to make a weak muscle have a less rigid bladder neck to push the urine through.

Thus, all types of vesical neurogenic disturbance in the male can usually be dealt with satisfactorily. Unfortunately, in the female the position is more difficult. No satisfactory urinal can be fitted and catheter life is always difficult and sometimes impossible. Because of the short urethra, incontinence is more common. The same principles apply as in the male but transurethral resection has to be much less radical because of the danger of incontinence and of fistula formation. Obstructive changes occur at the female bladder neck as in the male (Moore, 1952) and may make the inefficiency of the neurogenic bladder worse; transurethral resection may give good results. In the female paraplegic, however, with bed sores and severe leg contractures, urination is a difficult problem. There is little advantage in making the bladder empty efficiently into the bed. If the upper limbs are fairly normal one possible method of treatment is suprapubic transposition of the urethra as described by Griffiths (1960). When incontinence is a major symptom treatment is very difficult and in many is associated with a reflex bladder which leaks at frequent intervals, often associated with abdominal and lower limb contractions. The voluntary muscle contractions are now usually reduced or abolished by intrathecal phenol injections. In my view this helps if the bladder innervation is affected by the injection, as an atonic bladder usually results. Although this effect is usually temporary, by adequate dosage it could possibly be made permanent with great benefit. When all else fails the formation of an ileal conduit or an ileocæcal bladder may be advisable.

Many of the problems of incontinence due to neurogenic vesical disturbance are illustrated by the following patient reported by me some years ago (Moore, 1953, 1956).

Case II.—Mrs. N. F., aged 35. Transverse myelitis 1945—residual spastic paraplegia. First seen by me in 1950 because of incontinence. Investigations revealed a small, partly fibrous and partly spastic bladder associated with gross sepsis of the bladder and both kidneys. An attempt was made to close the urethra and treat the patient with permanent suprapubic drainage but this was unsuccessful. Eventually in 1952 an artificial bladder was made consisting of the ascending right half of the transverse colon into which both ureters were transplanted. The terminal ileum was brought out on to the abdominal wall as a urethra. A competent ileocæcal valve ensured urinary continence, the patient catheterized the artificial bladder every two to three hours during the day. To avoid any possibility of hyperchloræmic acidosis continuous catheter drainage was employed at night. Since this operation the patient has lived a useful life, resumed her occupation as a cashier and married. Although urinary function improved remarkably during the first two years after the operation there has been some recrudescence of the infection in both kidneys from time to time and stones have formed and have been removed from the artificial bladder. One year ago against my advice the patient became pregnant and the obstetrician allowed the pregnancy to continue. On July 31, 1959, the patient was delivered of a premature male child which unfortunately died after forty-eight hours.

Although it might be felt that this case is a tribute to modern surgical techniques it is also a condemnation of the modern treatment of the neurogenic bladder. In both sexes the conversion of a spastic reflex bladder to the non-reflex type, either by open rhizotomy or intrathecal phenol injections might be advantageous. Any inefficiency of bladder emptying by manual compression and abdominal straining could then, if necessary, be improved by transurethral resection of the bladder neck. If incontinence occurred in the female, some minor local procedure would probably be sufficient for continence between the times of suprapubic compression. It should always be essential to retain the bladder capacity. Even where this is not done, it might be worth enlarging the bladder capacity by ileocystoplasty. So far I have not carried out this procedure on the neurogenic bladder but have used it successfully in other types of bladder contracture.

Acknowledgments.—It is a pleasure to record my indebtedness to the following for their help: Dr. Fergus Fergusson and the staff of the Manchester University Department of Neurology,

particularly Dr. L. Liversedge; Mr. P. B. Clark, my Chief Assistant at the Manchester Royal Infirmary; Dr. R. G. W. Ollerenshaw and the staff of the Department of Medical Illustration, M.R.I.; and my successive House Surgeons, particularly Mr. Harvey Wacks.

REFERENCES

Bors, E. (1951) In: The Cyclopedia of Medicine. Eds.: G. M. Piersol and E. L. Bortz. Philadelphia; 9, 603.
—— (1957) *Urol. Surv.*, **7**, 177.
Damanski, M., and Gibbon, N. (1956) *Brit. J. Urol.*, **28**, 24.
Denny-Brown, D. E., and Robertson, E. G. (1933) *Brain*, **56**, 149.
Griffiths, I. H. (1960) *Brit. J. Urol.*, **32**, 27.
Lapides, J. (1957) In: Physiologic Principles of Surgery. Eds.: L. M. Zimmerman and R. Levine. Philadelphia and London; p. 825.
McLellan, F. C. (1939) The Neurogenic Bladder, Springfield, Ill.
Moore, T. (1952) *Proc. R. Soc. Med.*, **46**, 558.
—— (1953) *Lancet*, i, 1176.
—— (1956) *Brit. J. Urol.*, **28**, 410.
Munro, D. (1937) *Amer. J. Surg.*, **38**, 120.
Nesbit, R. M., and Lapides, J. (1948) *Arch. Surg., Chicago*, **56**, 139.
Petersen, I., and Franksson, C. (1955) *Brit. J. Urol.*, **27**, 148.
Prather, G. C. (1949) Urological Aspects of Spinal Cord Injuries, Springfield, Ill.
Ross, J. C. (1956) *Brit. J. Urol.*, **28**, 14.
Von Garrelts, B. (1956) *Acta chir. scand.*, **112**, 326.
—— (1957) *Acta chir. scand.*, **114**, 49.

Management of the Bladder in Congenital Spinal Cord Lesions [*Abridged*]

By D. Innes Williams, F.R.C.S.

London

Since the war, the study of the neurogenic bladder has received a tremendous impulse from the setting up of special units for the care of paraplegics. At these it has been demonstrated how much can be achieved in controlling micturition in these unfortunate individuals, and how well renal function can be preserved. It must not be assumed, however, that the same methods can be applied with success in cases of congenital spinal cord lesions: indeed an attempt to do so would give most disappointing results. In the paraplegic unit we are normally dealing with a fit adult male who has suffered a high traumatic lesion of the cord, and to a greater and greater extent we aim at a controlled bladder contraction with minimal residual urine. In the congenital cases we have to follow infants and children throughout growth, often with severe concomitant deformities of the lower limbs and practically always with low lesions which involve conus and spinal centre for micturition; with bladders, therefore, which do not achieve spontaneous co-ordinated contractions. More and more the tendency in recent years has been to divert the urine from ureteric level and to short-circuit the bladder altogether.

In the great majority there is an evident myelomeningocele with a variable degree of paralysis of the legs. A smaller number, however, have no external evidence of the spinal lesion and these are often purely sacral deformities with few signs in the lower limbs. The bladder disorder is then perhaps the only handicap in an otherwise healthy child. It is curious how often the significance of sacral agenesis is overlooked: in almost all of my 20 patients, the bony deformity has been completely missed by the physician first seeing the case and even when recognized it was not always appreciated that if 3 or more pieces of the sacrum were missing there must certainly be interference with the nerve supply of the bladder. All my cases of sacral agenesis had signs of neurogenic bladder since early infancy; by contrast, several examples of what I call sacral scoliosis and some of spina bifida occulta had a late onset of symptoms. This onset of incontinence is not necessarily evidence of a change in the nerve lesion, it may simply be a urinary infection which upsets a precariously balanced control. Nevertheless, the frequency of onset in later adolescence and early adult life does suggest that a neurological explanation is required.

Diagnosis usually presents no difficulty because of the obvious vertebral deformity and the coincidence of other neurological signs, particularly peri-anal anæsthesia and relaxation of the anal sphincter. No one of these signs is the inevitable concomitant of a neurogenic bladder, however, and I have had undoubted examples with normal anal tone without loss of sensation. Naturally a simple failure of fusion of the laminæ of the lower lumbar or sacral vertebræ is not considered evidence of a spinal cord lesion, and occasionally a child with such a minor deformity does have a trabeculated bladder with overflow incontinence in which it is hard to distinguish bladder neck obstruction from a neurological abnormality. However, the ready expressibility of the lower motor neuron bladder, and the failure of bladder neck resection to achieve any considerable improvement, usually settles the diagnosis.

The precise manifestations of the bladder abnormality vary considerably from case to case. It has proved almost impossible to correlate the type of bladder dysfunction with other evidence of the level and extent of the cord lesion. Many authors have used the cystometrogram as their

index of activity; they recognize the uninhibited, the automatic, the autonomous and the atonic neurogenic bladder. These are somewhat idealistic conceptions, however; in practice such clear-cut distinctions are seldom possible, and in general I do not find that the cystometrogram gives any useful information which cannot be obtained more satisfactorily from clinical observation, radiology and endoscopy.

Almost all these patients have lower motor neuron bladders, though in some neurological signs such as an up-going toe and absent abdominal reflexes indicate that the myelodysplasia affects a greater length of the cord than the bladder disorder would suggest. Exceptionally, the child complains of frequency, urgency and incontinence, often with difficulty in micturition, symptoms somewhat similar to those seen in disseminated sclerosis. These are rare, however; the true automatic bladder is not seen at all and the great majority would be classified as autonomous, or a few as atonic bladders. Almost all are partly or completely expressible, and if spontaneous micturition occurs it is with the aid of diaphragm and abdominal muscles. The really important differences lie in the degree of urethral resistance, the presence or absence of trabeculation and the degree of dilatation of the upper urinary tract.

At one extreme there are smooth-walled bladders without hypertrophy, with completely relaxed bladder necks, which never contain any considerable volume of urine. The urethral resistance is so low that no urine accumulates; there is no hope that such a child will develop control, but the upper tract remains in good condition because of the absence of back-pressure, and urinary infections are uncommon. With a slightly greater urethral resistance, but still a flaccid, smooth bladder, urine accumulates and can be expressed. In some fortunate children, more often girls, a balance can be achieved so that after complete expression there is no leakage for two or three hours and a control of sorts is thereby attained. This requires an intelligence and co-operation seldom reached before 7 or 8 years of age. As long as the bladder is atonic, upper tract dilatation is minimal, but with the passage of years some hypertrophy of the detrusor is the rule and often the competency of the uretero-vesical valve is lost, allowing reflux into the ureters. In time, therefore, the kidneys are damaged by back pressure.

Some children have heavily trabeculated bladders from early infancy; hypertrophy is in fact already present at birth. These may still be completely or partly expressible and may in the same way attain control. They are, however, much more liable to severe recurrent urinary infection and to upper tract dilatation; the ureters become enormous, tortuous, and ultimately rigid tubes. The renal parenchyma is slowly thinned out by hydronephrotic distension of the calyces and pyelonephritic scarring. The blood urea climbs steadily and if the child lives on into adolescence renal osteodystrophy is a common complication.

We are therefore faced with the twofold problem of incontinence and of renal failure, and there is no necessary correlation between the two. If there is no urethral resistance, continence is impossible, but the kidneys are preserved; while in cases where satisfactory expression gives a reasonable control there may be progressive failure of renal function.

Continence

The ideal is to achieve an expressible bladder which can be completely emptied and which will not allow leakage for two or three hours afterwards. In younger infants expression must be performed manually by the mother, later the child will do it by abdominal straining. If the urethral resistance is too high, expression will be incomplete, there will be a residual urine and dribbling will continue. In these circumstances it is first important to empty the rectum, an accumulation of hard fæces being the most common cause of a large residual urine. Urinary infection also makes expression more difficult. Bladder neck resection is helpful at times, but my experience with this operation is rather disappointing; only a few children have been helped.

Expression will also fail to give control if the urethral resistance is too low, urine will dribble out before a sufficient quantity has accumulated in the bladder. In boys this may be treated by a plication operation to build up the resistance of the bulb of the urethra. It has proved of great assistance where incontinence occurs only on exertion.

In girls I have not had such success with operations to support the urethra, though they have been reported as of value by some authors. The urethral resistance may be low only in relation to a hypertonic bladder, and if we could relax the detrusor we might obtain satisfactory expression. I have attempted to do this with Pro-Banthine in some children and although there has been perhaps a little improvement, none of the results has been dramatic. The number of children who attain continence by these means is not large but is perhaps larger than expected. When I surveyed a series of 65 patients some years ago I found that almost a third of those who had attained the age of 8 or 9 had reasonable control, though this group was highly selected and perhaps gives an unduly optimistic impression.

What then of the children in whom continence is not achieved? In the very young of both sexes there is no doubt that napkins and rubber pants are much the easiest method of coping with the flow of urine, though obviously great care must be taken to preserve the insensitive skin of the genitalia from excoriation. In girls who by the age of 8 or 9 show no signs of getting any sort of control, diversion of urine is essential, since no form of appliance has proved successful in collecting the urine, nor have any of the devices for compressing the urethra had any permanent success. The diversion which we favour at the moment is the urinary ileostomy. In boys, where we are dealing simply with incontinence, diversion is not always required. Appliances are difficult to fit to the very small penis but with the development of plastic materials it should not often be necessary to perform a loop operation in boys. After puberty, a portable urinal is reasonably satisfactory, though not always attractive. Some boys, however, have also to cope with calipers and other orthopædic appliances, which makes a portable urinal difficult to manage: they are then more comfortable with a urinary ileostomy. A sponge rubber penile clip seems crude, but leaves the child free from encumbrances; several active young men under my care wear it without discomfort and with satisfactory control. It should not be worn at night.

Renal Function

Important as it is to achieve urinary control, the preservation of renal function is of even greater importance to the health and life of the child. Those who survive the early hazards of meningitis and hydrocephalus are more likely to die of renal failure than anything else. The kidney is destroyed by pyelonephritis and hydronephrosis, but both result from obstruction to the urinary tract. The obstruction is not simply at the bladder neck or urethra and it is dysfunction of the bladder as a whole which must be considered. Unfortunately we do not know how to convert the spastic and dangerous type of bladder into one which is atonic and comparatively innocuous. Again we have to decide whether to preserve the bladder or to divert the urine. In the early stages resection of the bladder neck may improve bladder emptying, relieve back-pressure on the kidneys and allow recurrent infections to be controlled, but this operation has been disappointing in many children. In comparatively mild cases we may attempt to protect the upper urinary tract by preventing vesico-ureteric reflux. Reflux is common in the neurogenic bladder and when unilateral both hydronephrotic and pyelonephritic renal destruction is more advanced on that side. It seems logical, therefore, to prevent reflux if it can be done without adding obstruction. A variety of operations is now available, but it will be some years before we are able to say whether they are effective in preventing deterioration of the kidney. Recurrent infection can be controlled by continuous chemotherapy, by regular expression of the bladder and by attention to emptying the rectum.

In more advanced disease, renal deterioration can only be averted by diversion of urine, and for this purpose diversion at ureteric level is much more effective than cystostomy. An indwelling suprapubic tube in a trabeculated bladder is often the cause of gross sepsis, stone formation and chronic ureteric obstruction: it fails in its purpose of decompressing the kidneys. Indwelling urethral catheters are in general unsuitable for children and suffer the same disadvantages. The urinary ileostomy, draining both ureters through a conduit formed by an isolated loop of ileum on to the surface of the abdominal wall is effective if performed before the ureters have become grossly dilated and rigid. This operation has been in general use for only about five years, but has proved of considerable value. I have performed it 17 times in children with neurogenic bladders, and in about twice as many with other conditions. It has its complications, some of them tiresome, but I have had only one operative death and that in very advanced disease among my first attempts. The ileostomy bag is fitted without difficulty, is watertight, and is little handicap to active children: the stoma gives trouble from time to time due to stenosis, but minor adjustment serves to correct it.

Cutaneous ureterostomy without the interposition of an ileal loop was practised before the present technique was developed, and some did well. The operation still has a place where the ureteric dilatation and elongation is extreme: the ureters are then easily brought to the surface and the biochemical complications sometimes seen with an ileal loop and renal failure are avoided. In the absence of hydro-ureter, however, the tendency to stenosis at the stoma is very great.

In summary then my answer to the question "When should a urinary ileostomy be considered?" is as follows: If the upper urinary tract is normal and urine sterile, diversion should be performed when urethral incontinence becomes intolerable. In girls the operation is undertaken between 4 and 8 years; in boys only where penile urinals are impracticable. If the upper urinary tract is becoming increasingly dilated and urinary infection cannot be controlled by simple measures directed to the intact bladder, diversion should be performed at any age, whether in a 2-year old baby or in an adult whose incontinence is more or less controlled by regular expression.

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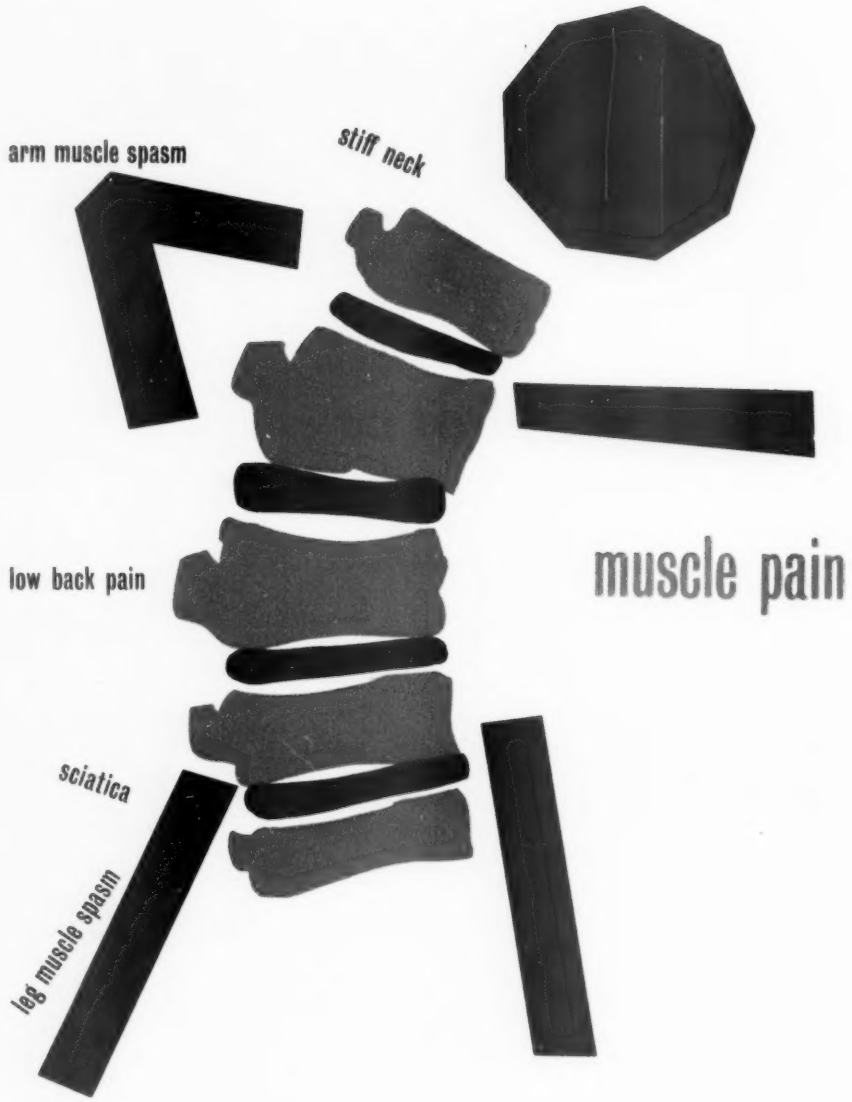
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Section of Odontology

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Meeting
January 25, 1960

Comparative Studies in Periodontal Disease [*Abridged*]

By B. COHEN, D.D.S., M.S.D., H.D.D.

London

ON the basis of histological studies reported previously (Cohen, 1959) the suggestion was put forward that periodontal disease in its most destructive form is initiated as a consequence of chronic ulceration in the interdental area. It was further suggested that the reason for the susceptibility of this area is that between teeth which erupt in contact, the interdental septum has the form of a col, the surface of which is covered by nothing more than the juxtaposition of the interproximal reduced enamel epithelia of the adjacent teeth. It was postulated that this enamel epithelium, being a vestigial tissue whose primary function had been discharged, was ill-fitted to act as an outer protective integument since it possessed neither the capacity for keratinization nor the ability to proliferate rapidly and extensively, both of which features are characteristic of stratified squamous epithelium.

It has previously been reported, notably by Skillen (1930), that periodontal disease is common in rats fed on laboratory diets. Skillen's finding that the awns of oats were frequently seen to have pierced the gum margin and injured the subepithelial tissues has been confirmed in the present investigation. It has repeatedly been found that foreign bodies, surrounded by an inflammatory reaction, are embedded in the periodontal ligament, sometimes even beneath the level of the alveolar crest. Unless serial sections were examined it was not always possible to relate these areas of periodontal injury to the existence of a breach in the overlying epithelial surface. The lack of this precaution could lead to the fallacious surmise that periodontal destruction had taken inception in alveolar bone or the periodontal fibres. When serial sections were examined, however, it was invariably found that a breach in the epithelial integument was present; moreover in every instance the injury could be traced to a surface covered by reduced enamel epithelium. It would appear that the stratified squamous epithelium of the oral mucosa is capable of resisting penetration by the sharp particles of the diet, but that the enamel epithelium is not similarly impervious to external assault.

Physical Constitution of Diet

The attempt was therefore made to determine whether or not the incidence of periodontal damage in laboratory rats was related to the constitution of the diet. Six litters of rats, thirty-six in all, were divided into two groups, one of which, the control group, was fed on normal laboratory diet and the other on a diet devoid of sharp particles. The normal diet consisted of tubular pellets, three-eighths of an inch in diameter, composed in the main of wheatmeal and ground oats with the addition of necessary vitamin supplements, and compounded into a form requiring considerable gnawing and mastication. The soft diet consisted of rindless cheese, soft bread, shelled hard-boiled egg, raw carrot, raw cabbage, and cooked horseflesh. Soon after weaning, rats were weighed at regular intervals and it was established that no great difference in the nutritional value of their different diets could be detected by this means. From the age of 3 weeks until 16 weeks rats were sacrificed from each group at weekly intervals and their jaws were removed for histological examination.

Differences between the experimental and control animals could be detected even in 3-week-old rats. Three differences were observed between the two groups as a whole: (*a*) Keratinization of oral epithelium appeared to be more marked in the control animals; (*b*) the state of eruption seen in the controls was usually in advance of that seen in their experimental littermates; M3 was always present at 30 days in the control rats, but its eruption had not been completed in most of the experimental animals; (*c*) finally, and of most interest, the periodontal tissues were incomparably healthier in the rats which had been maintained on a diet of soft food.

Figs. 1, 2, 3 and 4 illustrate the difference seen in litter-mates at the age of only 35 days. Fig. 1 shows the molar region of a rat fed on bland food; the interdental areas are normal in appearance. In Fig. 2, taken from a rat fed on the harsh diet, it is obvious that considerable destruction of the interdental epithelium has occurred and an inflammatory reaction can be observed in the underlying tissues. Figs. 3 and 4 extend this

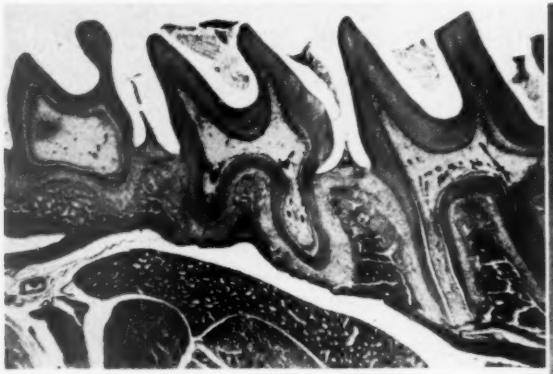


FIG. 1.—Molars of 35-day-old rat fed on soft food. Note healthy interdental septa. H. & E. ×13.

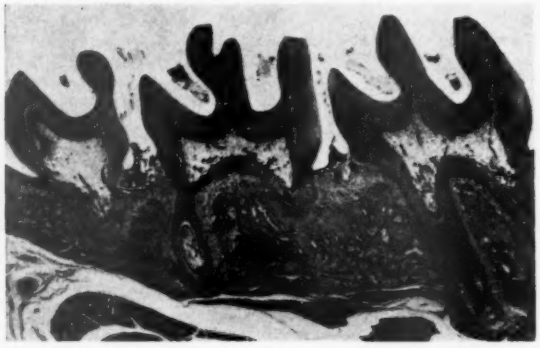


FIG. 2.—Molars of 35-day-old rat fed on normal laboratory diet. Note damaged interdental septa. H. & E. ×13.

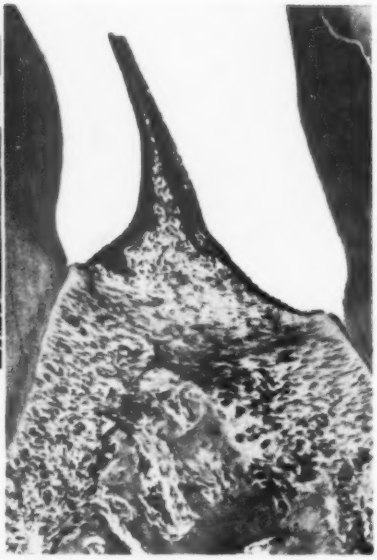


FIG. 3.—Septum between M2 and M3 from rat on soft diet (Fig. 1). H. & E. ×92. →

FIG. 4.—Septum between M2 and M3 from rat on hard diet (Fig. 2). H. & E. ×92.

comparison with a view of the respective areas between M1 and M2 under higher magnification.

The difference in degree of keratinization, if significant, could probably be attributed to the difference in abrasiveness between the two diets. The difference in eruption times constitutes an incidental finding illustrating what may be an interesting side-effect of dietary constituents.

The fact that young rats maintained on the diet of soft constituents were invariably less affected by periodontal disease was a striking finding. At a very early age periodontal damage could be observed in the control animals. Whether or not their oral epithelium was more heavily keratinized, the presence of foreign bodies in their subepithelial tissues was a constant finding. Keratinization of the oral epithelium was evidently a factor of no consequence, because it was not the oral epithelium which was breached by the food particles or hairs that were found lodged in the fibres of the periodontal ligament. In every case the breach in the outer epithelial integument could be traced to the enamel epithelial surface;

FIG. 5.—Retromolar papilla, 63-day-old rat. Enamel epithelium lacerated by a foreign body. H. & E. ×92.

Fig. 5, which is a section of the retromolar papilla of a 9-week-old rat, provides a typical illustration of enamel epithelium lacerated by a spear-shaped fragment. It was remarkable that even in 3- and 4-week-old rats extensive periodontal damage was already present, and in some instances this had occurred so soon after the emergence of the first cusp that severe septal inflammation could be observed even before the crown of the erupting tooth had emerged in its entirety. Such a circumstance is illustrated in Fig. 6 which shows the molar teeth of a 22-day-old rat fed on laboratory diet. It will be observed that M2 is not completely erupted and yet the interdental septum between M1 and M2 already shows signs of serious damage (*see* Fig. 7).

In the older rats it was observed that the difference in health between the control and experimental rats became somewhat less marked, although at all stages it remained true that the control rats were far more susceptible to periodontal breakdown. The impression that the disparity in health between the two groups lessened with advancing age was derived from two factors: first, that in the rats which have suffered early damage a certain degree of healing can be effected as gingival recession takes place, if the damage has not extended too deeply; second, that some periodontal damage, albeit not severe, is to be seen in the older rats maintained on a soft diet. These two factors will now be discussed in detail.

The Healing Process

The protective function of the squamous epithelium constituting the surface of the oral mucous membrane is repeatedly illustrated in histological studies from rats fed on the mechanically injurious laboratory diet. The site of ingress of sharp particles into the subepithelial periodontium can almost invariably be related to

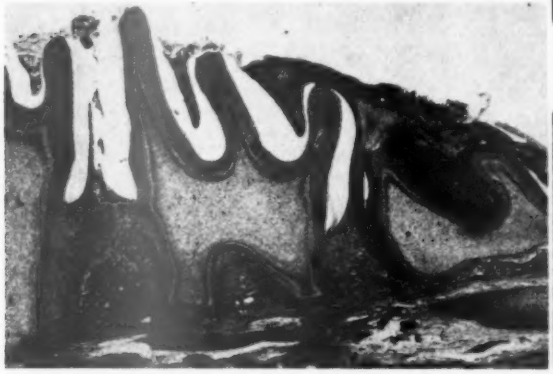


FIG. 6.—Molars of 22-day-old rat. Note that eruption of M2 is incomplete but septum between M1 and M2 is already damaged; for detail *see* Fig. 7. H. & E. ×17.

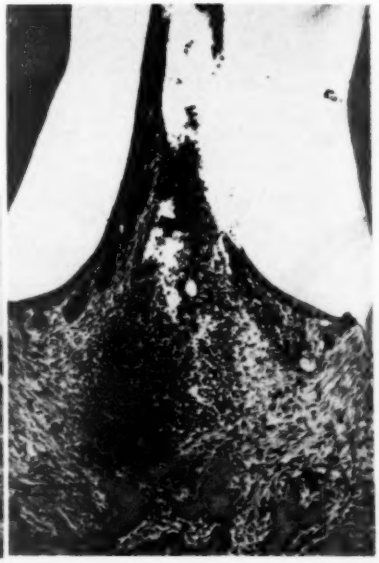


FIG. 7.—M1 and M2 from Fig. 6 showing destruction of the enamel epithelium and an intense inflammatory reaction extending down to the level of the alveolar crest. H. & E. ×92.

FIG. 8.—Retromolar papilla from a 63-day-old rat. OE — Oral epithelium. EE — Enamel epithelium. FB—Foreign body. H. & E. ×92.

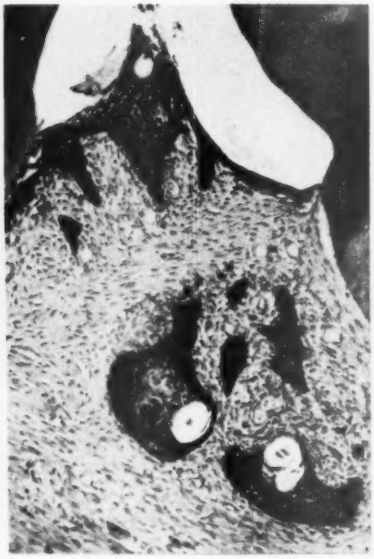


FIG. 9.—Rat interdental septum showing foreign bodies surrounded by stratified squamous epithelium deep within the periodontal ligament. H. & E. ×92.

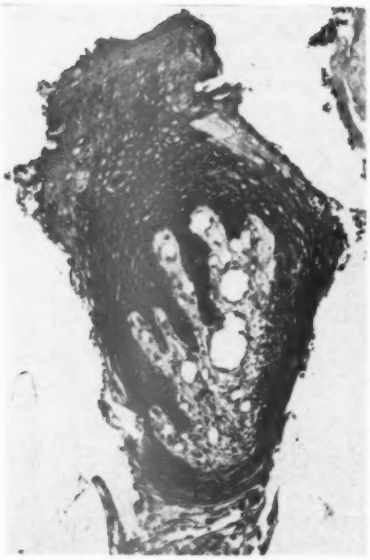
FIG. 10.—Septum on mesial side of erupting molar in monkey. EE — Interproximal enamel epithelium. CA —Contact area. OE—Overlying oral epithelium. H. & E. ×28.

the surface distribution of enamel epithelium, but in many instances such damage appears to have elicited a purposeful proliferation on the part of the stratified squamous epithelium. A good example of this response is shown in Fig. 8, where foreign material occupies a site deep to the retromolar gingival sulcus—a common occurrence in the material studied and one in which an associated breach in the enamel epithelium can invariably be demonstrated. In this particular illustration it is noteworthy that proliferation of oral epithelium along the connective tissue aspect of the enamel epithelium has taken place to an extent far greater than is normally seen in a rat of this age. The purpose of such epithelial proliferation appears to be to surround and extend beneath the foreign body and so once more to fulfil the primary epithelial function of insulating the internal environment from external assault. Fig. 9 is one of many examples which could be chosen to illustrate this striking facility of stratified squamous epithelium for encompassing foreign bodies in the corium, but it has not been possible to demonstrate that enamel epithelium possesses such a propensity to more than a very limited degree.

A circumstance such as the above indicates that the integrity of the periodontium, even though it be imperilled by the ineffectual defence of enamel epithelium on its surface, can be retrieved in those situations where oral epithelium abuts upon the vulnerable enamel epithelium. This would seem to provide a reasonable explanation for the fact that the most severe chronic periodontal pockets are seldom seen originating on buccal/labial or lingual aspects, but are usually located interdentally.

Periodontal Damage in Rats on Soft Diet

Where the injurious effect of harsh particles in the diet has been precluded, the periodontal structures are still occasionally subjected to the subepithelial impaction of foreign material. In this instance the injurious element is hair, which is often present in the mouth in considerable quantity, being introduced, presumably, in the course of the animal's ablutions. Loose hairs tend to accumulate between the teeth, and single shafts are capable of penetrating enamel epithelial surfaces and setting up an inflammatory reaction in the underlying tissues. A further complicating factor seen in older animals, which also serves to facilitate the lodgment of loose hairs, is the accumulation of food debris around the teeth in the rats fed on soft foods. Some years ago Rushton (1951) showed that the accumulation of



←FIG. 11.—Higher magnification of OE from Fig. 10. H. & E. ×92.

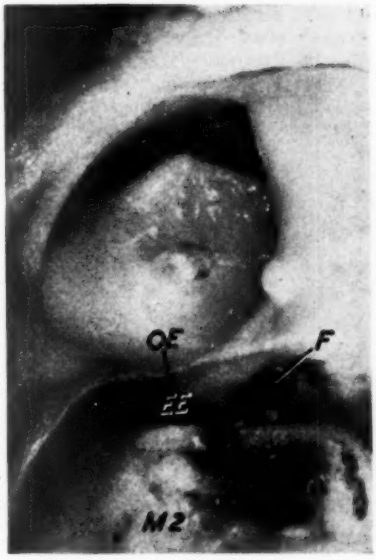


FIG. 12.—Human second molar (M2) and erupting third molar, photographed after decalcification. OE—Overlying oral epithelium. EE—Interproximal enamel epithelium. F—Fenestration of EE at point of contact of two teeth. *See* text and compare Fig. 10. ×3. →

plaque material on the teeth of hamsters could be reduced by the incorporation of abrasive matter in the diet, and the same feature can be illustrated in the present study by a comparison between rats receiving soft and coarse diets.

Briefly, the effect of this dietary experiment upon the periodontal tissues of rats could be summarized as follows: The diet containing sharp particles affected the periodontium deleteriously and severe damage was often seen in young rats; some of this damage was progressive, but when superficial it could apparently be arrested, or at least slowed down, by the localizing action of the inflammatory process and by downgrowth of stratified squamous epithelium. Rats maintained on a diet free of mechanically irritant particles were far less prone to early damage; in older animals minor ulceration and varying degrees of periodontal inflammation were associated with the accumulation of food debris around the teeth and the impaction of hairs in the soft tissues.

It is important that the distinction between hard foods and injurious elements should not be overlooked. The better periodontal state of the rats on bland food is attributable not to the soft nature of their diet but only to the absence of sharp particles. Indeed deleterious effects of soft constituents became apparent in later age groups, where the accumulation of food debris around the teeth was considerably less in the control rats; presumably the mastication of coarse food had the effect of cleansing tooth surfaces.

The Application of these Studies

The application of these studies to clinical situations encountered in human subjects is clearly limited. Not only are there material differences in the shape and contact areas of rat and human molars, but the nature of the human diet cannot be compared to that which has been shown to be injurious to rats; moreover the practice of oral hygiene has, in a proportion of cases at least, marched in step with evolutionary ascent. Nevertheless there is a definite implication of an origin in epithelial inadequacy, as Fish (1935) originally suggested. The proximity of stratified squamous epithelium may well determine the course of events once an initial breach in the surface has been effected. So far as periodontal disease in humans is concerned the chance that such a breach may result from particulate matter in the diet is unlikely, in the case of an interdental origin, for two reasons: first, the fact that our diet is normally devoid of such particles; and second, that the area is normally well protected from the assaults of sharp spicules by the contact of two teeth above it.

The Nature of the Interdental Injury in Humans

In the absence of an obvious traumatic agent such as has been identified in the case of laboratory rats, some other source of the initial interdental injury must be sought. It was previously surmised on the basis of histological observations that a breach in the integrity of the oral epithelium must necessarily occur interdentally at the time of eruption of a tooth into contact with a neighbour-

ing tooth already present in the mouth. Detailed scrutiny of erupting teeth at a microscopical level was therefore undertaken.

It has previously been shown, in mesiodistal as well as buccolingual sections cut through the col between two teeth in contact, that an area devoid of oral epithelium could be demonstrated interdentally. It was felt necessary, however, to detect the occurrence of this defect during the course of eruption in order to support the hypothesis as to its origin. It would therefore be necessary to identify a situation in which the interproximal enamel epithelium of the erupting tooth had come into juxtaposition with that of the neighbouring tooth already present in the arch; and in which the bridge of oral epithelium was still present above these adhering enamel epithelia. A precise phase in the eruption process would be necessary in order to demonstrate this particular feature, and the paucity of human material available in this age group necessitated recourse to the examination of monkeys. Serial sections were examined of an interdental area between molar teeth at the stage where contact had been established between the erupting tooth and its neighbour. Fig. 10 shows that an exact phase in the predicted phenomenon can be demonstrated. The two interproximal enamel epithelia have come into apposition, back to back, and above this conjunction the bridge of oral epithelium, now no more than an attenuated strand, can be seen in cross-section. Its appearance when viewed under higher magnification (Fig. 11) discloses a degree of degeneration that foretells its early disintegration. Some cells are pyknotic, some vacuolated, and the corium upon which the epithelium necessarily depends is depleted almost to vanishing point. This is an appearance which has been duplicated in many other monkey specimens examined. In order to confirm that the bridge of oral epithelium does in fact undergo disintegration it is necessary only to examine sections taken from a slightly later stage of eruption when, although the juxtaposition of adjacent enamel epithelia is still in evidence, the strand of doomed epithelium above the contact point is no longer to be seen.

A similar arrangement of the tissues can be seen in human material. Fig. 12 is a photograph of the upper left second and third molars, the latter in an early stage of eruption, removed from a male aged 16 years. After fixation the specimen was decalcified, and examined under a dissecting microscope. It can be seen that the oral epithelium exists as a thin strand between the buccal and lingual papillæ. The deeper portion of the interdental septum, made visible by the dissolution of enamel, is constituted by the interproximal enamel epithelia of the two molars. The tight contact between the two teeth had been identified by X-ray examination prior to decalcification, and it can be seen that the septum has become fenestrated in this area. It will readily be appreciated that with the continuation of upward movement of the third molar this breach is likely to extend and the development of an interdental septum having the form of a col awaits only the breakdown of the slender strand of oral epithelium at present continuous above the contact area.

It is believed that the above observations lend support to the hypothesis put forward previously to the effect that the eruption of contiguous teeth is inevitably associated with an interdental breach in the oral epithelial integument, and that this defect can come to constitute the site of initiation of a periodontal pocket.

One of the curious effects of the destruction of interdental oral epithelium in the course of tooth eruption concerns the gingival crevice, which has been defined as the potential space existing between an erupted tooth and the epithelium which surrounds it. If it be accepted that in the normal crevice at least part of this epithelium is stratified squamous, it follows that the crevice does not extend into an interdental area denuded of oral epithelium during eruption. In view of the evidence suggesting that the presence or absence of oral epithelium is a factor of considerable prognostic significance, it may be useful to draw a distinction between lesions *originating in the col* and those *originating in the crevice*. It is the former type which is likely to take a rapid course, to progress intractably, and to develop into the clinical feature referred to as an intrabony pocket. In the crevicular variety, however, an initial lesion occurring at or near the confluence of oral and enamel epithelium may be inhibited from progressing by the protective proliferation of oral epithelium; it is for this reason that periodontal disease originating in the crevice is more readily amenable to treatment, and is likely to involve the deeper structures and the supporting bone only in those cases where the normal tissue defence mechanism is deranged by gross neglect or by the presence of systemic disease.

Acknowledgments.—I am grateful to Sir Wilfred Fish in whose Department, and with whose help, this research is being carried out. I am obliged to Mr. E. B. Brain for the illustrations to this paper. This work has been done during the tenure of a Leverhulme Fellowship in Oral Pathology.

REFERENCES

COHEN, B. (1959) *Brit. dent. J.*, **107**, 31.
FISH, E. W. (1935) *Brit. dent. J.*, **58**, 531.
RUSHTON, M. A. (1951) *Brit. dent. J.*, **90**, 87.
SKILLEN, W. G. (1930) *J. Amer. dent. Ass.*, **17**, 645.

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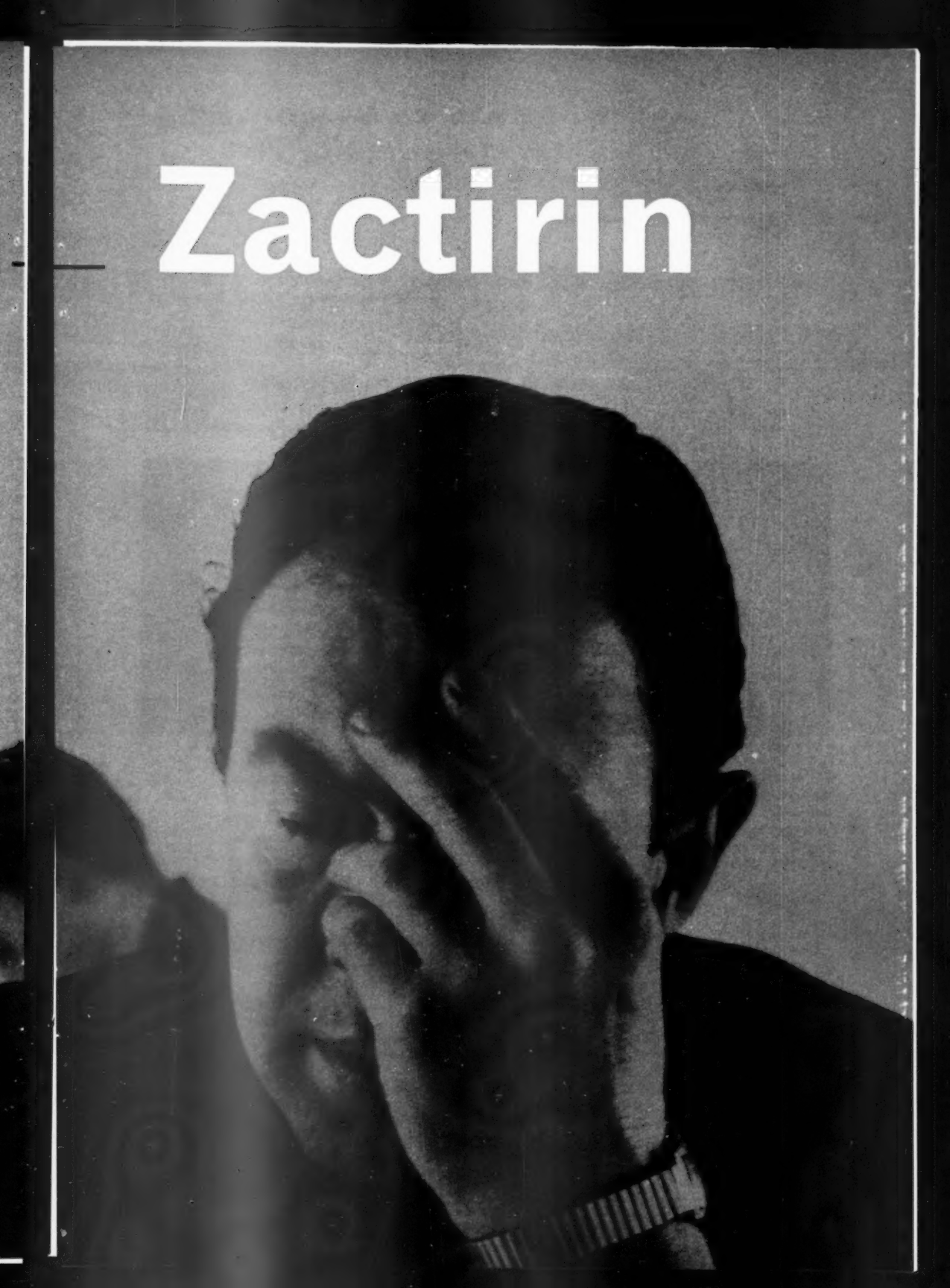

Section of Comparative Medicine

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Meeting
October 21, 1959

Mr. M. CRAWFORD delivered his Presidential Address entitled **Information and Library Services in Relation to Medical and Veterinary Science.**

Meeting
December 16, 1959

DISCUSSION ON SENECIOSIS IN MAN AND ANIMALS

Professor Kenneth R. Hill (London):

The World-wide Distribution of Seneciosis in Man and Animals

Seneciosis is a disease caused by the ingestion of certain plants which cause liver degeneration and necrosis. Such plants belong to the genus senecio (Compositæ) and in this country include such examples as ragwort and groundsel. Similar hepatotoxic properties have been observed following the ingestion of crotalaria (Leguminosæ) and heliotropium (Boraginaceæ) and in consequence the condition produced by all three species has been given the generic term "seneciosis". These genera contain alkaloids of the pyrrolizidine group which on hydrolysis usually yield necic acid and amino alcohols (necines) (Henry, 1949; *Research Today*, 1949).

Hepatic Veno-occlusive Disease (V.O.D.)

In Jamaica Dr. K. Rhodes and I (Rhodes, 1957) studied a disease in young children, previously described by McFarlane and Branday (1945) and Royes (1948), which was characterized by acute liver enlargement and ascites, often progressing to early cirrhosis. One of the main pathological features of this condition was partial or complete occlusion of the centrilobular veins and the smaller hepatic vein tributaries. Although these pathological changes resemble those found in Chiari's disease (Chiari, 1899), we called the condition hepatic veno-occlusive disease (V.O.D.) (Bras and Hill, 1956). Blockage of the centrilobular veins gives rise to intense congestion and engorgement and, if chronic, results in a centrilobular cirrhosis similar to that seen following chronic venous congestion due to heart failure (cardiac cirrhosis).

The evidence that V.O.D. is caused by the senecio group of alkaloids is circumstantial. Many of the "bush teas", or infusions of plants, drunk for medicinal purposes in the West Indies, are toxic. Some children in Barbados who were found by liver biopsy to have V.O.D. had been given infusions of crotalaria (Stuart and Bras, 1956). Subsequently, Berry and Bras (1957) produced V.O.D. in a calf by feeding *Crotalaria fulva*, and Hill *et al.* (1958) have produced V.O.D. in the rat both by the injection of monocrotaline (one of the pyrrolizidine alkaloids) and by feeding ragwort (*S. jacobæa*). In 1929, Hays and VanEs reproduced the "walking disease" of horses and cattle by feeding *Senecio ridelli* and re-examination of the livers of these animals (Hill and Martin, 1958) has shown that at least one characteristic lesion is hepatic veno-occlusive disease. As long ago as 1918, Theiler produced thickening of the centrilobular venous walls in cows and horses by feeding *Crotalaria dura*, and his description, in our opinion, is that of V.O.D.

In man seneciosis is not confined to Jamaica. In South Africa Stein (1957) has confirmed V.O.D. in 4 patients, and in 1951 Selzer and Parker reported a case of Chiari's syndrome due to senecio poisoning. Histological slides from India have shown the presence of V.O.D. (Bras and Hill, 1956), and I have also seen a case from Israel. The conditions described by Wurm (1939) in Germany and by Hashem (1939) in Egypt also suggest V.O.D.

Seneciosis in Animals

Seneciosis in animals has been known for many years and has a world-wide distribution. In the Americas it has been described in the West Indies in cows (Bras and Berry, 1956), as the "walking disease" of horses and cattle in Nebraska (Hays and VanEs, 1929), and as Pictou disease in Nova Scotia (Pethick, 1906); it also occurs in swine (Emmel *et al.*, 1935), chickens (Neal and Becker, 1933), quails and doves (Thomas, 1934), and in horses and goats (Emmel and Sanders, 1942). In Europe, the natural disease has been encountered in the United Kingdom in horses and cattle (Evans and Evans, 1949; Forsyth, 1954; Betty and Markson,

1954), in Norway (Slagsvold, 1933), in Czechoslovakia as the Zdar disease of horses (Vaněk, 1957), and in Germany as Schweinsberger disease of horses (Santave, 1958). In South Africa seneciosis has been known for many years as "Dunziekte" in horses and cattle (Theiler, 1918); in New Zealand, as Winton disease (Gilruth, 1902); in Australia, in horses, cattle as "walkabout" disease, and in sheep (Murnane and Ewart, 1928; Bull, 1955); and in Japan (Ueda and Ohbayashi, 1953).

Markson and I have examined material from horses and cattle poisoned with ragwort and have found the presence of V.O.D. Similarly V.O.D. has been found in horses suffering from the "walking disease" (Hill and Martin, 1958), and in cows in Jamaica believed to have had seneciosis (Bras and Berry, 1956). Examination of the reports and photographs of the publications of Theiler (1918) in South Africa and Bull (1955) in Australia leaves no doubt that one aspect of seneciosis described by these authors is V.O.D.

Pathogenesis of Veno-occlusive Disease

One theory is that V.O.D. is the result of spasm of the centrilobular vein (as found in anaphylaxis) which may subsequently produce an intimal œdema and obstruction such as that described in serous hepatitis (Roessle, 1943). There is as yet little evidence for this. Another theory is that the condition is due to thrombosis, with subsequent organization leading to venous blockage.

A constant finding is centrilobular hæmorrhagic necrosis, and in some of the material from South African patients, kindly sent to me by Stein, this was prominent. The experimental production of V.O.D. in the rat by injecting monocrotaline and retrorsine, or by the ingestion of ragwort, is also accompanied or preceded by a centrilobular hæmorrhagic necrosis. Histologically, a deposition of fibrin can be clearly demonstrated and this seems to stimulate a marked proliferation of the endothelial cells lining the intima. These proliferated cells probably have fibroblastic properties, for they appear to give rise to a loose collagenous reticulum, occluding the vein. Whether or not these endothelial cells become fibroblastic is still under investigation, but such a metamorphosis has been postulated before (Altschul, 1954).

An interesting feature of experimental studies in the rat is the production of hepatocellular megalocytosis, bile duct hyperplasia and cirrhosis, in addition to the hæmorrhagic necrosis and V.O.D. Whether the liver cell enlargement has a different pathogenesis from the necrosis or whether it is a time-dose phasic difference we are unable to say at present. But this condition, called "megalocytosis" by Bull (1955), is found constantly in the naturally occurring disease in animals and occasionally in humans, and is considered by some to be the most important aspect of seneciosis: ultimately seneciosis may be the cause of cirrhosis and a possible cause of neoplastic change (Schoental *et al.*, 1954; Schoental and Magee, 1959; Dybing and Erichsen, 1959). Hirchinson in my laboratory has added varying concentrations of monocrotaline to tissue cultures of human embryo liver cell lines and has produced degenerative conditions with megalocytosis resembling those of the natural and experimental disease.

So far experimental evidence suggests that the effect of the pyrrolizidine group of alkaloids is *directly* hepatotoxic and that hæmorrhagic necrosis, V.O.D., megalocytosis and cirrhosis are consequences of this hepatotoxicity rather than four distinct entities.

Acknowledgment is made of the grants-in-aid from the Lederle Laboratories Division, the Josiah Macy Junior Foundation, and Nutrition Foundation, the Board of Governors of the Royal Free Hospital, London, and the British Empire Cancer Campaign; also to Dr. R. Adams of the University of Illinois for the supplies of monocrotaline.

REFERENCES

ALTSCHUL, R. (1954) Endothelium. New York.

BERRY, D. M., and BRAS, G. (1957) *N. Amer. Vet.*, **38**, 323.

BETTY, R. W., and MARKSON, L. M. (1954) *Vet. Rec.*, **66**, 398.

BRAS, G., and BERRY, D. M. (1956) *W. Ind. med. J.*, **5**, 37.

——, and HILL, K. R. (1956) *Lancet*, ii, 161.

BULL, L. B. (1955) *Aust. vet. J.*, **31**, 33.

CHIARI, H. (1899) *Beitr. path. Anat.*, **26**, 1.

DYBING, O., and ERICHSEN, S. (1959) *Acta path. microbiol. scand.*, **47**, 1.

EMMEL, M. W., and SANDERS, D. A. (1942) *Pr. Bull. Fla. agric. Exp. Sta.*, No. 577.

——, ——, and HENLEY, W. W. (1935) *J. Amer. vet. med. Ass.*, **86**, 43.

EVANS, W. C., and EVANS, E. T. R. (1949) *Nature, Lond.*, **164**, 30.

FORSYTH, A. A. (1954) British Poisonous Plants H.M.S.O., London; Bull. No. 161.

GILRUTH, J. A. (1902) Div. vet. Sci., New Zealand. Rep. Dept. Agric, 1.

HASHEM, M. (1939) *J. Egypt. med. Ass.*, **12**, 1.

HAYS, C. H., and VANES, L. (1929) On the nature, cause and possible prevention of the "walking disease" amongst horses and cattle. Dept. of Agriculture, State of Nebraska, Lincoln, Nebraska, U.S.A.

HENRY, T. A. (1949) The Plant Alkaloids. 4th ed. London.
HILL, K. R., and MARTIN, H. M. (1958) *Brit. vet. J.*, **114**, 1.
——, STEPHENSON, C. F., and FILSHIE, I. (1958) *Lancet*, i, 623.
MCFARLANE, A. L., and BRANDAY, W. J. (1945) *Brit. med. J.*, i, 838.
MURNANE, D., and EWART, A. G. (1928) Council for Scientific and Industrial Research, Commonwealth of Australia Bull. No. 38.
NEAL, W. M., and BECKER, R. R. (1933) *J. agric. Res.*, **47**, 617.
PETHICK, W. H. (1906) Special Report on Pictou Cattle Disease. Dept. Agric., Ottawa; 90.
Research Today (1949) Senecio and Related Alkaloids. Lilly Research Lab., Indianapolis.
RHODES, D. (1957) *W. Ind. med. J.*, **6**, 1.
ROESSLE, R. (1943) *Virchows Arch.*, **311**, 252.
ROYES, K. (1948) *Caribbean med. J.*, **10**, 16.
SANTAVE, Von F. (1958) *Planta med.*, **6**, 78.
SCHOENTAL, R., HEAD, M. A., and PEACOCK, P. R. (1954) *Brit. J. Cancer*, **8**, 458.
——, and MAGEE, P. N. (1959) *Acta Un. int. Cancr.*, **15**, 212.
SELZER, G., and PARKER, R. G. F. (1951) *Amer. J. Path.*, **27**, 885.
SLAGSVOLD, L. (1933) *Norsk Vet. Tidsskr.*, **45**, 329.
STEIN, H. (1957) *Brit. med. J.*, i, 1496.
STUART, T. K., and BRAS, G. (1956) *W. Ind. med. J.*, **5**, 33.
THEILER, A. (1918) 7th and 8th *Rep. vet. Res. S. Afr.*, p. 8.
THOMAS, E. F. (1934) *J. Amer. vet. med. Ass.*, **85**, 617.
UEDA, A., and OHBAYASHI, M. (1953) *Jap. J. vet. Sci.*, **15**, 109.
VANĚK, J. (1957) *Rev. Czech. Med.*, **3**, 1.
WURM, H. (1939) *Klin. Wschr.*, **18**, 1527.

Mr. L. M. Markson (Weybridge):

The Pathogenesis of the Hepatic Lesion in Calves Poisoned Experimentally with Senecio jacobæa

Now that the relationship between the various species of senecio, crotalaria and heliotropium and the intoxication they cause in livestock has been generally recognized, seneciosis has become an agricultural rather than a veterinary problem, with the practical emphasis shifted from the poisoned animal to grazing management and weed control. Nevertheless the reaction of animals to pyrrolizidine alkaloids, either isolated or in plants, presents a fascinating problem.

It is generally agreed that the alkaloids are essentially hepatotoxic, the systemic disease being due to hepatic dysfunction. The hepatic lesions of seneciosis are exemplified in *Senecio jacobæa* poisoning in cattle and consist of variations in the size and shape of parenchymal cells, variable fibrosis, often pericellular or causing inverse lobulation, chronic endophlebitis of centrilobular and hepatic veins and bile duct proliferation.

In the past the pathogenesis of seneciosis was studied at necropsy on animals with naturally occurring or experimental disease, the sequence of events being reconstructed from the terminal picture. On this basis the picture was interpreted as representing post-necrotic scarring with bile duct proliferation and parenchymal megalocytosis (although that word was not used) indicative of attempted regeneration, an interpretation which I myself used to accept (Betty and Markson, 1954). Theiler (1918) described centrilobular hæmorrhage as the first stage in the process, in so far as it led to parenchymal necrosis. More recently Bull (1955) used the word "megalocytosis" to describe the enlargement of parenchymal cells which he considered the primary and pathognomonic feature of poisoning by pyrrolizidine alkaloids. The resulting increased death-rate of the parenchymal cells led to the other histological features. Bras *et al.* (1954) have described a comparable disease in Jamaican children, which was subsequently thought to be due to the ingestion of crotalaria extracts in the form of "bush tea". They stressed the centrilobular venous lesion, coining the term veno-occlusive disease (V.O.D.), and reinterpreted Theiler's centrilobular hæmorrhage as passive hyperæmia. Discussing equine seneciosis Vaněk (1956) considered "the effect of the alkaloids to be hepatotoxic and not capillarotoxic. . . . The changes in hepatic veins are not primary but result during the localisation of necrosis round these veins".

Description of Experiments

I have administered dried *Senecio jacobæa* or an aqueous extract to calves while following the sequence of hepatic events in serial biopsy samples of liver. Several calves received subtoxic doses of the alkaloids, one was killed in an early stage of the hepatic disease and three in a late stage. A description of the hepatic histology in two animals from the latter group illustrates the progression of the disease.

Calf 681. Initial weight 170 kg. It was intended to feed 5 lb (2·25 kg) ragwort hay daily, but this had to be reduced within a week to 2½ lb (1·13 kg) and even that amount was not always eaten regularly. About 36 lb (16·2 kg) (equivalent to 5·6 g alkaloids) were consumed in the first twenty days of the experiment, after which the calf refused more.

Slight parenchymal steatosis was seen in the liver biopsy taken three weeks after the beginning of the experiment. At four weeks, by which time the calf was very ill, parenchymal steatosis, considerable bile duct proliferation, a general increase of reticulin

and endothelial proliferation and degeneration with early fibrosis in centrilobular veins were concurrently present. By five weeks these lesions were severe and the bile duct proliferation quasicarcinomatous. V.O.D. could be seen, but megalocytosis was difficult to recognize as so many parenchymal cells were swollen with fat droplets. The calf was killed two days later when on the verge of coma.

Calf 694, initial weight 182 kg, ate about 20 lb (9·1 kg) of ragwort hay in the first twenty days and about 27½ lb (12·5 kg) (equivalent to 4·2 g alkaloids) in thirty-seven days.

Slight parenchymal steatosis was seen at two weeks. At three weeks the following were visible: bile duct proliferation with peribiliary cirrhosis; endothelial proliferation and necrosis in centrilobular veins with early reticulin and collagen fibrosis in the proliferating intima; moderate parenchymal steatosis and megalocytosis. A week later V.O.D. was present, as well as extensive, diffuse fibrosis disrupting the normal lobulation pattern. Weekly biopsies were taken until the calf was killed nine weeks and two days after the start of the experiment. At autopsy the hepatic changes were confirmed, the V.O.D. being more obvious than in the biopsies.

Discussion

Bearing in mind that there may be differences in the reaction of different animal species to different plant species, and that differences in total alkaloid dosage and rate of dosage will affect the hepatic reaction, my few cases of *S. jacobæa* poisoning in calves do not support any of the theories put forward about the pathogenesis of seneciosis. The total hepatic picture is comparable, but not the sequence of events. The earliest changes were slight, parenchymal steatosis. A week later bile duct proliferation, parenchymal cell changes, diffuse fibrosis and centrilobular endophlebitis appeared to be developing concurrently. Centrilobular hæmorrhage and necrosis were not seen. It may be that subtler techniques would have demonstrated even earlier changes in the parenchymal cells; but there is nothing in these biopsy samples of liver to suggest that the parenchymal cell changes were the cause of the other lesions.

Investigating the hepatotoxicity of retrorsine for the rat, Davidson (1935) suggested that the alkaloid first accumulated in the parenchymal cells and was later released into the centrilobular and hepatic veins where it caused swelling and proliferation of the venous endothelial cells. It may be that in my cases the alkaloids first accumulated in the parenchymal cells to the detriment of the latter and were subsequently released into the hepatic venous system, causing veno-occlusive disease, and the bile, causing proliferation of the bile ducts. At least parenchymal cell changes, V.O.D. and bile duct proliferation all appear to be primary lesions and not contingent on one another. The diffuse fibrosis may be in part post-necrotic, in part supportive to the proliferating bile ducts. That it may also be a primary response to the alkaloids cannot be ruled out.

Acknowledgment is made to Dr. Regina Schoental for the alkaloid analyses.

REFERENCES

BETTY, R. W., and MARKSON, L. M. (1954) *Vet. Rec.*, **66**, 398.
BRAS, G., JELLIFFE, D. B., and STUART, K. L. (1954) *Arch. Path., Chicago*, **57**, 285.
BULL, L. B. (1955) *Aust. vet. J.*, **31**, 33.
DAVIDSON, J. (1935) *J. Path. Bact.*, **40**, 285.
THEILER, A. (1918) 5th and 6th *Rep. vet. Res. S. Afr.*, p. 9.
VANĚK, J. (1956) *Sborn. čes. Akad. zemědělsk. Ved.*, **29**, 705.

Dr. Regina Schoental (Carshalton):

The Chemical Aspect of Seneciosis

It is almost half a century since it was first recognized that the toxicity of some senecio plants and their ability to cause liver damage in livestock is due to their alkaloidal constituents (Cushny, 1910–11). Since then, in addition to the genus senecio (Compositæ), many other plants such as crotalaria (Leguminosæ) and heliotropium (Boraginaceæ), have been found to contain similar hepatotoxic alkaloids.

Structure of Pyrrolizidine Alkaloids

The chemistry of these alkaloids has been clarified in the last twenty-five years by four groups of workers, led by Menshikov in the U.S.S.R., Roger Adams in the U.S.A., Warren in Natal and Culvenor in Australia. The alkaloids are derivatives of pyrrolizidine, which consists of two fused five-membered rings inclined to each other, with a nitrogen at one point of their fusion (Fig. 1). About 50 pyrrolizidine

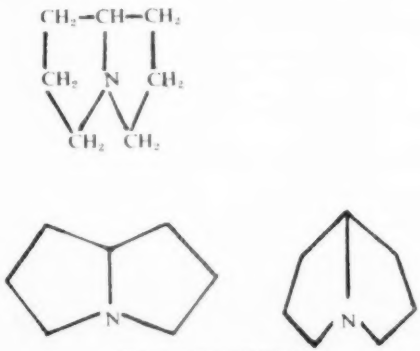
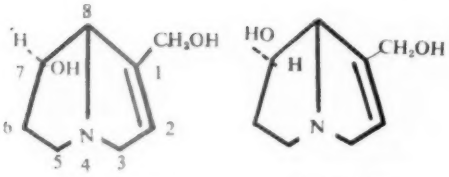


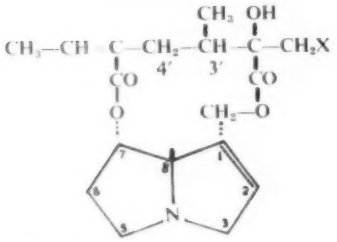
FIG. 1.—Pyrrolizidine.



Retronecine Heliotridine

FIG. 2.

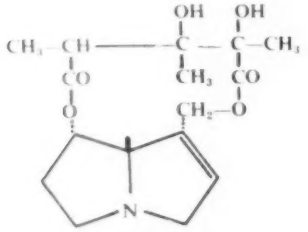
CYCLIC ESTERS



X = OH; Retrorsine (cis).

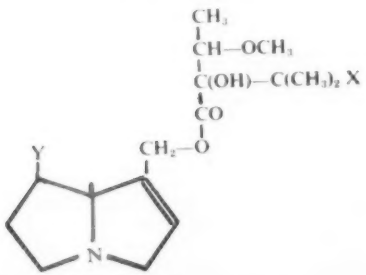
X = OH; Riddelliine —double bond present at $C_{3'}:C_{4'}$.

X = H; Seneciphylline (cis) double bond present at $C_{3'}:C_{4'}$.



Monocrotaline

OPEN ESTERS



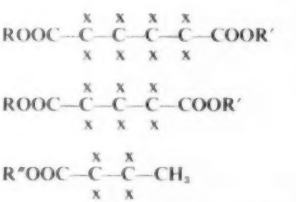
X = H; Y = OH; Heliotrine.
X = OH; Y = $CH_2CH:C(CH_3)COO$; Lasiocarpine.

FIG. 3.—Examples of hepatotoxic pyrrolizidine alkaloids.

alkaloids have already been described, but not all are hepatotoxic (*see* reviews by Warren, 1955; Adams and Gianturco, 1957; Culvenor, 1958; Schoental, 1957).

The alkaloids known to be hepatotoxic are all esters of 1-hydroxymethyl-1 : 2-dehydro-7-hydroxy-pyrrolizidines (Fig. 2) with various branched-chain, hydroxylated or unsaturated acids, known as necic acids, having 4, 5 or 6 carbon-chains. Neither the free basic moieties, the necins, obtained by hydrolysis of the alkaloids, the free acids, nor a mixture of both are hepatotoxic. The position of the hydroxymethyl-group is fixed due to the double bond at carbons 1 : 2, but the hydroxyl attached to the asymmetric carbon at position 7 can be either *endo*, in retronecine, or *exo*, in heliotridine.

When this hydroxyl is in the *endo* position cyclic esters with dicarboxylic acids can be formed without strain. The alkaloids from most of the senecio and crotalaria plants contain retronecine as the basic moiety (Fig. 3). In the case of senecio the acids are usually substituted adipic acids, while in crotalaria they are substituted glutaric acids. The alkaloids of heliotropium plants, so far described (e.g. Culvenor, 1954; Culvenor *et al.*, 1954; Crawley and Culvenor, 1956), are open esters of heliotridine (in which the hydroxyl at position 7 is *exo*) or of supinidine (which lacks this hydroxyl altogether) with substituted monocarboxylic, four carbon-chain acids. The substituents of the necic acids (Fig. 4) can be hydroxy, methoxy, methyl,



X = H; CH_3; OH; OCH_3; $CHCH_3$; $CH(CH_3)_2$, etc.

R R′ = retronecine.

R″ = heliotridine.

FIG. 4.

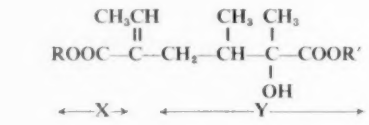
isopropyl, vinyl, and other groups; some of the acids are unsaturated but all have branched-chains. The significance of the individual substituents in relation to the hepatotoxic activity of the alkaloids has not yet been clearly defined.

A particular plant may contain more than one alkaloid. In some species there are five or more closely related alkaloids and these are usually

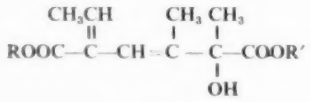
accompanied by their respective oxidation products, the more palatable *N*-oxides. The latter often constitute the predominant part of the alkaloidal constituents and resemble the parent alkaloids in their hepatotoxic action. Being more palatable they are likely to be the cause of livestock poisoning in the fields. The two forms of the alkaloids, oxidized and reduced, are readily interconvertible depending on the red-ox potential of the biological systems.

The amount and the relative proportions of the individual alkaloids in the plant may vary depending on the season, the stage of growth and the climatic and soil conditions (Crawley and Culvenor, 1956). They also vary in different parts of the plant, the leaves, seeds, or roots. The isolation and purification of individual alkaloids often present considerable difficulties: several alkaloids, originally described as pure entities, have been proved by the newer methods of chromatography and infra-red spectroscopy to be mixtures.

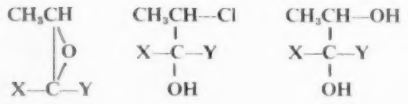
The alkaloids from ragwort, *Senecio jacobæa* L., are a good example of the difficulties encountered. Originally Manske (1931) isolated one alkaloid, jacobine. Later Barger and Blackie (1937) described three alkaloids and Bradbury and Culvenor (1954) six, all esters of retronecine. The structures and the close interrelationships of the acidic moieties of five of these alkaloids (Fig. 5) have been clarified only recently by Geissman (1959) and Bradbury and Masamune (1959). The structure of the acid of the sixth alkaloid, jacozine, still awaits elucidation.



Senecionine



Seneciphylline



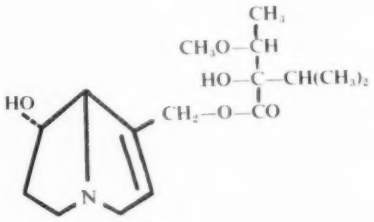
Jacobine Jaconine Jacoline

X = ROOC only.

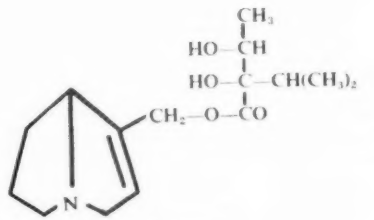
FIG. 5.—Alkaloids of *Senecio jacobæa* L.

Toxicity of Pyrrolizidine Alkaloids

Among the hepatotoxic alkaloids (Fig. 3), the cyclic diesters are most potent, a single oral dose of 30–50 mg/kg body weight being sufficient to produce subacute and chronic liver lesions in weanling Wistar rats; twice as much of the open diester, lasiocarpine and four times as much of the open monoester heliotrine are needed to produce similar effects (Schoental and Magee, 1959). The open monoester, supinine, which differs from heliotrine by the absence of the hydroxyl at C-7 (Fig. 6), was reported not hepatotoxic (Rose *et al.*, 1959). However, Bull and Dick (1959) showed more recently that this alkaloid can produce liver lesions, but the dose required is about 10 times that of the cyclic diesters and about twice that of heliotrine.



Heliotrine



Supinine

FIG. 6.

From a comparison of active and inactive pyrrolizidine alkaloids we can deduce some of the features necessary for the hepatotoxic activity. The double bond between carbons 1 : 2 of pyrrolizidine is indispensable; platyphylline, which differs only by its absence from senecionine,

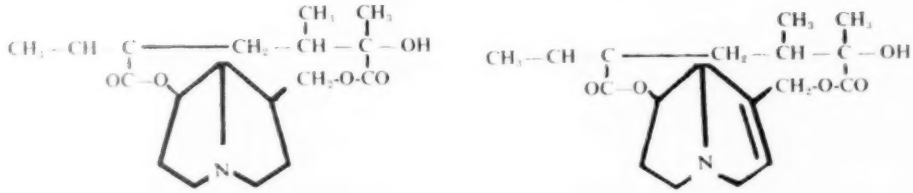


FIG 7.

is inactive (Fig. 7) as is rosmarinine, which has an additional hydroxyl at position 2 (Warren, 1956).

The essential biochemical lesion underlying the toxic effects of these alkaloids is unknown. It is possible that further elucidation will follow the preparation and study of appropriately labelled hepatotoxic analogues of the natural alkaloids. There are no natural pyrrolizidine alkaloids with straight-chain acids, but semi-synthetic alkaloids which are open diesters of retronecine with a series of simple, straight and branched-chain, acids (Fig. 8) have been pre-

Open diesters of retronecine with the acids:

Butyric $CH_3—CH_2—CH_2—COOH$

Valeric $CH_3—CH_2—CH_2—CH_2—COOH$

Isovaleric $CH_3—CH(CH_3)—CH_2—COOH$

Senecioic $CH_3—C(CH_3)=CH—COOH$

Tiglic $CH_3—CH=C(CH_3)—COOH$

FIG. 8.—Semi-synthetic alkaloids.

pared by Dr. A. R. Mattocks. The base used was natural retronecine obtained by hydrolysis of monocrotaline, isolated from *Crotalaria retusa* L. (obtained from Ghana through the kindness of Dr. C. D. Adams, Department of Botany, Achimota, and Dr. R. A. E. Galley, of the Tropical Products Institute, London). These compounds were tested in rats by the single-dose procedure (Schoental and Magee, 1957). The compounds with straight-chain acids were inactive but those with branched-chain acids proved hepatotoxic and produced cytological abnormalities of the parenchymal liver cells similar to those seen at corresponding times after treatment with the natural alkaloids (Schoental and Mattocks, 1960).

Thus, considerable variations in the size and structure of the acidic moieties of the alkaloids are compatible with hepatotoxic activity. One feature common to all the necic acids and to the acids of the hepatotoxic semi-synthetic analogues is branching of the carbon chain. Such structures could conceivably yield isoprenoid units. Isoprene units, derived from mevalonic acid (3 : 5-dihydroxy-3-methyl valeric acid) (Fig. 9) can be incorporated *in toto* into squalene, a precursor of cholesterol (Cornforth *et al.*, 1958) and possibly into steroid hormones and into terpenoids, such as vitamins A, K and E. The alkaloids may therefore interfere in some way with the biosynthesis of similar compounds in the animal body. That young sexually immature rats are more susceptible to the hepatotoxic action of the alkaloids than adult animals, and males more susceptible than females (Ratnoff and Mirick, 1949; Schoental, 1959) is suggestive of steroid metabolism involvement. But the necic acids as such are inactive. It may be that they are excreted or metabolized too readily, but that when esterified their excretion is delayed or their absorption facilitated so that they are available at the site of further biosynthetic processes. The basic moiety may have, however, a more fundamental role in the action of the alkaloids which are known to produce liver and lung lesions and even primary liver tumours

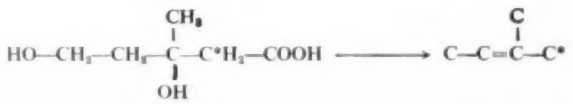


FIG. 9.

(Schoental *et al.*, 1954). The most impressive lesions caused by the alkaloids are the cytological abnormalities of the liver parenchymal cells which led Schoental and Magee (1959) to consider the alkaloids interphase mitotic poisons. Recently, Clark (1959) found heliotrine to be mutagen for drosophila. A possible action of the alkaloids might be an interference in carboxylase activity, in which biotin has been shown to play such an essential role (Lynen *et al.*, 1959). Structurally, there is some similarity between the "scaffolding" of biotin and pyrrolizidine alkaloids. The basic moieties of both contain two fused five-membered rings inclined to each other.

REFERENCES

ADAMS, R., and GIANTURCO, M. (1957) *Angew. Chem.*, **69**, 5.

BARGER, G., and BLACKIE, J. J. (1937) *J. chem. Soc.*, 584.

BRADBURY, R. B., and CULVENOR, C. C. J. (1954) *Aust. J. Chem.*, **7**, 378.

——, and MASAMUNE, S. (1959) *J. Amer. chem. Soc.*, **81**, 5201.

BULL, L. B., and DICK, A. T. (1959) *J. Path. Bact.*, **78**, 483.

CLARK, A. M. (1959) *Nature, Lond.*, **183**, 731.

CORNFORTH, J. W., CORNFORTH, R. H., POPJAK, G., and GORE, I. Y. (1958) *Biochem. J.*, **69**, 146.

CRAWLEY, H. C., and CULVENOR, C. C. J. (1956) *Aust. J. appl. Sci.*, **7**, 359.

CULVENOR, C. C. J. (1954) *Aust. J. Chem.*, **7**, 287.

—— (1958) In: Current Trends in Heterocyclic Chemistry. Edited by A. Albert *et al.* London: p. 103.

——, DRUMMOND, L. J., and PRICE, J. R. (1954) *Aust. J. Chem.*, **7**, 277.

CUSHNY, A. R. (1910–11) *J. Pharmacol.*, **2**, 531.

GEISSMAN, T. A. (1959) *Aust. J. Chem.*, **12**, 247.

LYNEN, F., KNAPPE, J., LORCH, E., JÜTTING, G., and RINGELMANN, E. (1959) *Angew. Chem.*, **71**, 481.

MANSKE, R. H. G. (1931) *Canad. J. Res.*, **5**, 651.

RATNOFF, O. D., and MIRICK, G. S. (1949) *Johns Hopk. Hosp. Bull.*, **84**, 507.

ROSE, C. L., HARRIS, P. N., and CHEN, K. K. (1959) *J. Pharmacol.*, **126**, 179.

SCHOENTAL, R. (1957) *Nature, Lond.*, **179**, 361.

—— (1959) *J. Path. Bact.*, **77**, 485.

——, HEAD, M. A., and PEACOCK, P. R. (1954) *Brit. J. Cancer*, **8**, 458.

——, and MAGEE, P. N. (1957) *J. Path. Bact.*, **74**, 305.

——, —— (1959) *J. Path. Bact.*, **78**, 471.

——, and MATTOCKS, A. R. (1960) *Nature, Lond.*, **185**, 842.

WARREN, F. L. (1955) *Fortschr. Chem. org. Naturst.*, **12**, 198.

—— (1956) Personal communication.

Meeting
February 17, 1960

MEETING AT ST. MARY'S HOSPITAL MEDICAL SCHOOL, LONDON

THE following demonstrations were given:

The Estimation of Free Plasma Serotonin.—T. M. ANDREWS, W. S. PEART and J. I. S. ROBERTSON.

The Organ of Jacobson: An Accessory Nose.—A. d'A. BELLAIRS.

Some Features of the Microscopic Anatomy of Freckles (Ephelides).—A. S. BREATHNACH.

The Structure and Biological Control of Cockroaches.—E. CAMERON.

The Reactions of Rat Lymph Nodes to Sublethal Radiation.—E. H. COOPER and E. L. ALPEN.

Histochemical Demonstration of Glycogen in Liver Tissue fixed for Electron Microscopy.—C. FOSTER.

Different Types of Allergy to Insects.—A. W. FRANKLAND.

An Effect of Temperature upon Wallerian Degeneration in Mammalian Peripheral Nerve Fibres.—H. J. GAMBLE.

Collagen Formation in Subcellular Fractions.—N. M. GREEN, D. A. LOWTHER and J. A. CHAPMAN.

Examples of Testicular Tumours in Different Species.—J. GUTHRIE.

The Effect of Hypoxia on Newborn Kittens and on Adult Guinea Pigs.—JUNE R. HILL.

Comparative Fœtal Growth Rates.—A. ST. G. HUGGETT and J. S. B. FRAZER.

Alkaline Phosphatase Studies of White Cells.—B. J. LEONARD.

Spontaneous Diabetes in Man and His Domestic Pets.—H. KEEN and J. WILKINSON.

Graft against Host Reactions in the Rabbit.—K. A. PORTER.

A Case of Toxoplasmosis.—D. M. PRYCE.

Effect of Analgesic Drugs on the Lens of the Eye.—MARTA WEINSTOCK, H. C. STEWART and K. R. BUTTERWORTH.

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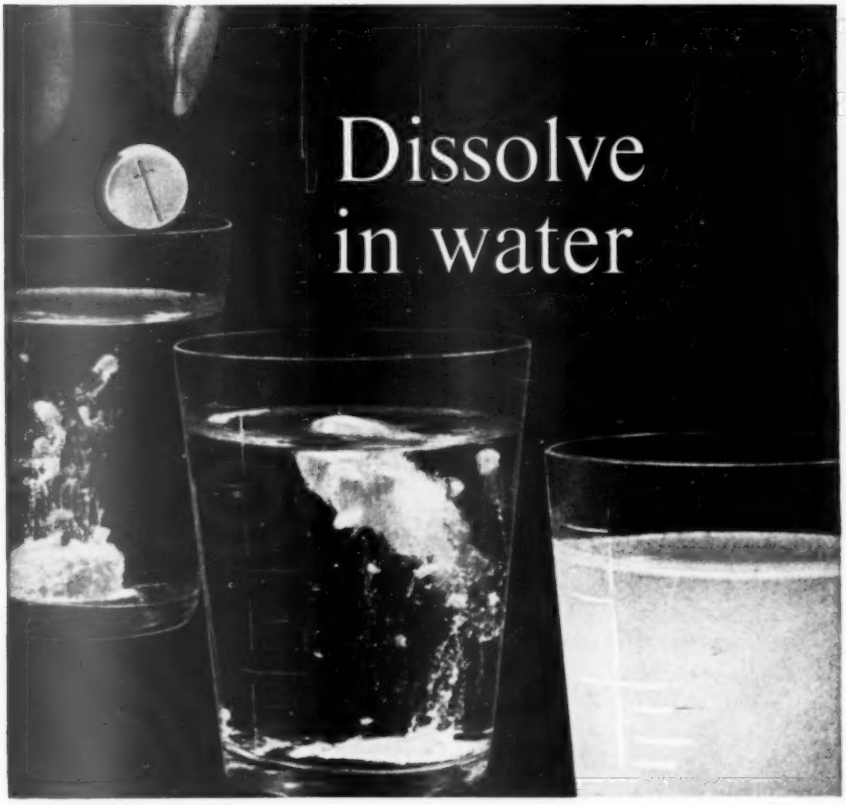

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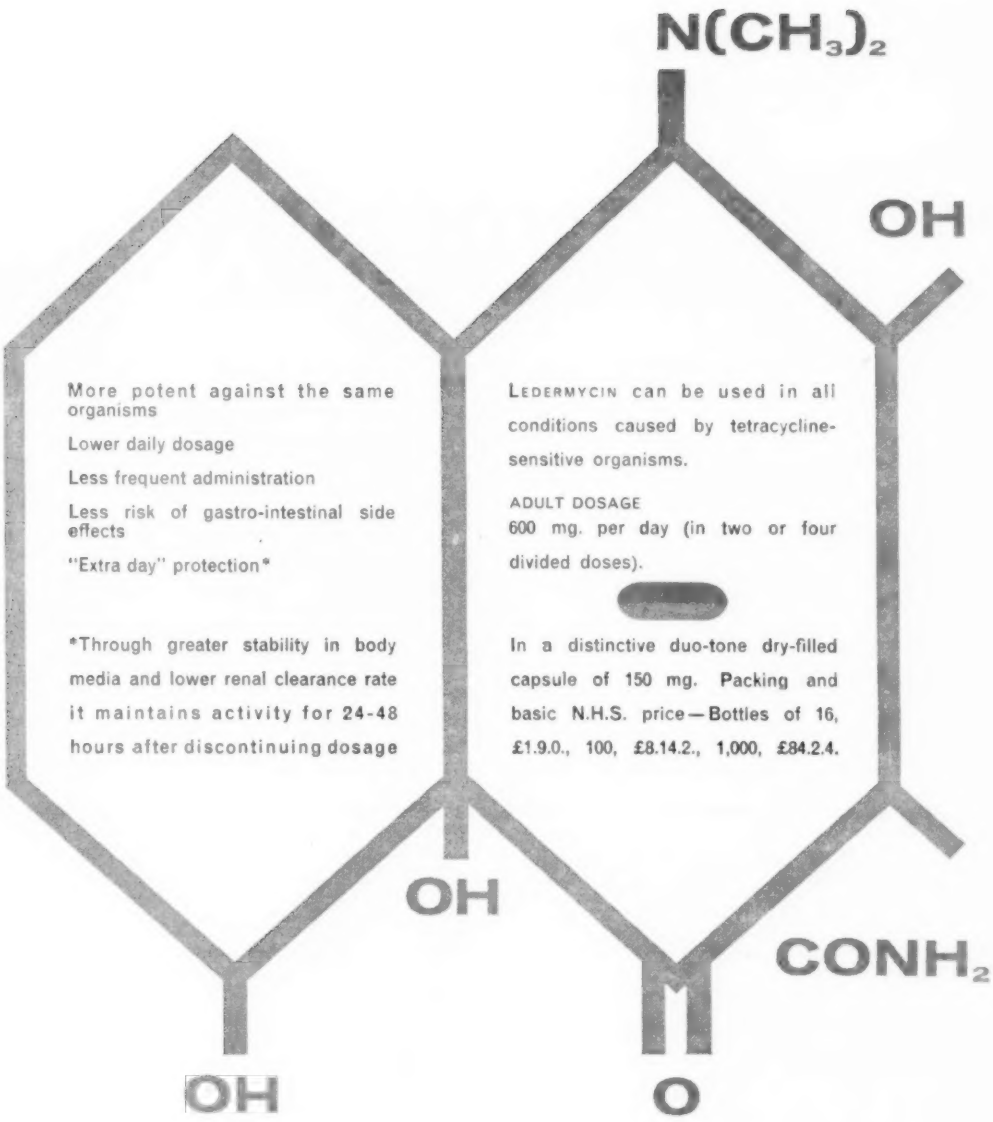

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Proceedings of the Royal Society of Medicine Vol. 53 289

Section of Anæsthetics

President—J. Alfred Lee, F.F.A. R.C.S., D.A.

Meeting
December 4, 1959
(contd. from March *Proceedings*, p. 188)

Rediscovery of Air for Anæsthesia in Thoracic Surgery[1]

By H. F. Poppelbaum, M.D.
Democratic Sector of Berlin, Germany

When the Allied troops established the second front in June 1944, they were equipped with anæsthetic apparatus which delivered controllable, known concentrations of ether/air, or of chloroform/air mixtures. As these were relatively simple, easily portable devices, requiring neither heavy gas-cylinders nor soda lime absorbers, transport problems did not arise.

At the anæsthetic symposium of the German Academy of Sciences in 1957 the question of anæsthetic apparatus utilizing air was again taken up. On this occasion some speakers claimed that the use of air was justified only under normal physiological conditions but not in the conditions obtaining during anæsthesia and operations. This attitude decided us to study the application of air as the exclusive vehicle for anæsthetic vapours such as ether, chloroform or halothane during transpleural thoracic operations. Our decision was based on the principles of controlled ventilation, as it seemed logical that patients who had been made apnœic by relaxants could be effectively ventilated with air mixtures in the same way as is done with oxygen-rich mixtures, as long as an adequate minute volume could be ensured.

We developed a relatively simple and adequate ventilation device in the shape of a double bellows for performing positive-negative pressure ventilation: the appliance is equipped with clearly visible non-return valves, and functions as an open system without any rebreathing (Fig. 1). The pressures obtainable with this appliance are in the range from plus 20 to minus 15 cm water, while minute volumes of over 10 litres can be obtained. Analysis of expired air with the Haldane apparatus always gave CO_2 concentrations below 3 vol.%. Measurements of minute volumes were carried out with a Dräger respirometer, or with a Douglas bag.

In contrast to ventilation with positive pressures alone, the following features of positive/negative pressures were considered to be valuable:

(1) The lowering of the mean ventilation pressure results in an improvement of the hæmodynamics of the patient; (2) the method practically overcomes the flow resistance of the breathing system and thereby (3) diminishes the functional residual air which results in improved CO_2 elimination. (4) The ventilation is improved by about 30% compared with positive pressure inflation using similar peak pressures. For the reasons set out above, complications such as hypoxia or hypercapnia which may easily occur in a closed or semi-closed anæsthetic system are no longer possible so long as an adequate minute volume is supplied.

Most anæsthetists are not in a position to use continuously recording appliances for checking the actual composition of the gas mixture contained in a closed circuit apparatus at any time. How many of us have any knowledge of the concentrations of anæsthetic agents such as ether or halothane in a closed circuit system at

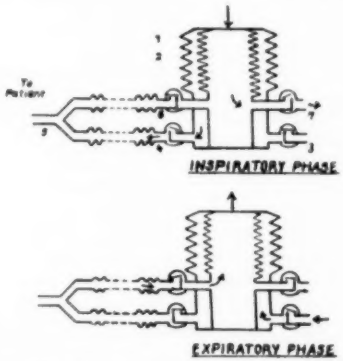

Fig. 1.—When compressing the double bellows, the contents of the outer chamber pass through the lower valve on the left to the patient, while the contents of the inner chamber are blown out to the atmosphere through the upper valve on the right. When pulling up the bellows, air is sucked from the lungs into the inner chamber while fresh air mixed with anæsthetic vapour is drawn into the outer chamber. 1. Outer (inspiratory) chamber of double bellows. 2. Inner (expiratory) chamber of double bellows. 3. One-way inlet valve for fresh gases. 4. One-way inspiratory valve. 5. Y-connexion to patient. 6. One-way expiratory valve. 7. One-way outlet valve for expired gases.

[1]These investigations were carried out in the Department of Anæsthetics and Bronchology at the Tuberkulose-Forschungsinstitut, Berlin-Buch. I am greatly indebted to Dr. H. G. Epstein (Oxford) for his translation and friendly advice.

any time during the operation? While we can measure the flows of oxygen, nitrous oxide or cyclopropane admitted to a closed circuit and thus have some control of these gases, in the case of vapours such as ether or halothane most of us can be guided only by the reactions of the patient.

Since the days of John Snow, anæsthetists have known that the safety of an inhalation anæsthetic depends to a large extent on the ease with which its concentration can be controlled and limited. Throughout the history of anæsthesia there have been many attempts to construct appropriate vaporizers which would deliver known concentrations of the anæsthetic vapour. One of these found widespread use not only in the British Army from 1941 onwards, but also with many civilian anæsthetists throughout the world; I refer to the Oxford vaporizer. As many of the younger generation of anæsthetists may never have seen this well-known device I mention only that in it the temperature of the liquid anæsthetic was maintained at a constant level by means of a chemical thermostat using hot water as the primary heat source.

The clinical investigations reported here were carried out originally with such vaporizers, but in more recent years with one of the well-known E.M.O. inhalers. No attempt is made in this new inhaler to maintain the liquid anæsthetic at a constant temperature. A known, controllable vapour concentration is ensured by the use of a thermo-compensator which alters the proportion of air passing through the vaporizing chamber of the inhaler according to the temperature of the liquid anæsthetic. This important simplification has become possible because anæsthesia nowadays no longer requires the high concentrations which could be taken from the former Oxford vaporizer. E.M.O. inhalers are available not only for ether but also for chloroform, trichlorethylene, halothane and more recently also for the so-called azeotropic mixture of ether with halothane.

In order to maintain normal adults during major surgical procedures at a level of anæsthesia corresponding to Guedel's third stage, first plane, a maintenance concentration of 5 vol.% ether is often quoted. After prolonged administration of such concentrations, the patient regains consciousness within ten to fifteen minutes. We found that for thoracic operations still lower ether/air concentrations in conjunction with muscle relaxants are often quite adequate, and return to consciousness is then correspondingly faster. When using such low and, more important still, perfectly uniform concentrations one does not meet with the complication of vomiting which was so widespread in former days of ether anæsthesia. By very gradual increase of ether concentrations, swallowing, vomiting and laryngeal spasm can be avoided during induction.

I mention in passing another practical aspect of ether/air mixtures. Many anæsthetists do not realize that mixtures of 5% ether (or less) in air do not detonate, although they may combust when ignited by a suitable source. On the other hand, ignition of mixtures with similar ether concentrations in *oxygen* would result in a detonation with disastrous consequences. The small risk of a mild deflagration with an ether/air mixture does not deter us from using it in the presence of surgical diathermy, but we usually provide a tube to lead away the exhalations from the field of operation (Fig. 2). Up to last summer we have been able to carry out thoracic operations with this method on over 250 patients, 200 with ether and 50 with halothane. Here I will only summarize a series of 100 anæsthetics which were carried through with careful oximetric studies (Table I). These patients were premedicated with pethidine 100 mg, atropine 0·5 mg, and

TABLE I.—100 THORACIC CASES VENTILATED WITH AIR

Pneumonectomy	4
Double lobectomy	2
Lobectomy	33
Lobectomy and segmental resection	4
Segmental resection	37
Resection and thoracoplasty	11
Thoracotomy	8
Extrapleural pneumothorax	1
Total	100

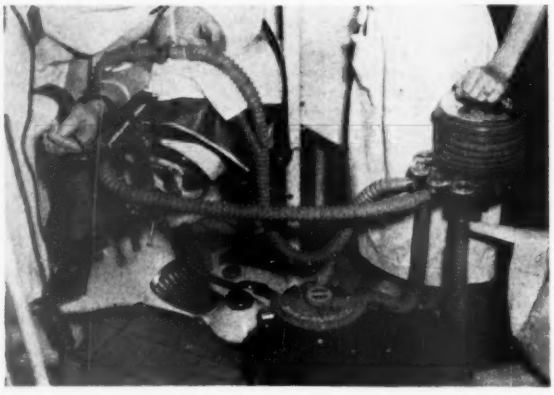

FIG. 2.—The main components of this arrangement are: the double bellows, the E.M.O. inhaler, tubes leading to the patient as well as a third tube for passing the expired gases outside the operating theatre.

promethazine 50 mg. Anæsthesia was induced with an intravenous barbiturate and intubation was facilitated by the use of a relaxant; further doses of curare were given as required.

During all these operations we measured the relative oxygen saturation of blood by means of an Atlas oximeter; at the same time we recorded the respiration of both lungs by means of two pneumotachographs which were connected to the two limbs of a Carlens tube (Fig. 3). In

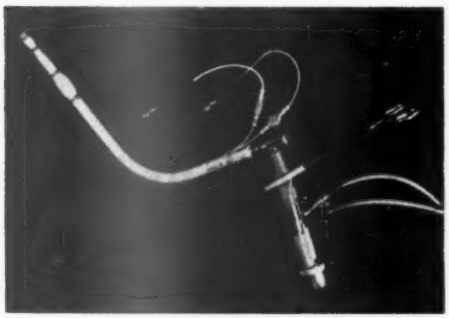

FIG. 3.—Small pneumotachographs attached to the two branches of a Carlens tube; tubes lead from them to a recorder. The clamp occluding one branch is shown in position.

order to avoid the objection that our patients might show a prolonged, raised oxygen saturation following preliminary inhalation of pure oxygen, we never administered any oxygen-rich mixtures while patients were undergoing oximetry. For that reason we were not in a position to set the absolute oxyhæmoglobin concentrations on our oximeter. We assumed arbitrarily a value of only 80% saturation for the patient breathing air alone. There is no doubt that the true values were in all cases appreciably higher. This does not detract from the significance of our observations on changes in oxygen saturation.

These oximeter curves obtained while ventilating both lungs during resections showed a very steady oxygenation value throughout anæsthesia with air as the vehicle; as the curves show, there was, of course, an initial temporary fall of oxygen saturation during the process of intubation. In normal clinical practice this fall is and always should be easily prevented by a short inhalation of oxygen preceding intubation (Fig. 4). Other small falls below the normal level occurred occasionally near the end of operation when we let the patient breathe spontaneously. In order to show the response of the oximeter we introduced a few intervals without ventilation; this also helped us to study the rate of return of oxygenation to normal values after the ventilation was resumed. Any deficient ventilation is clearly shown by an immediate decrease of oxygen saturation when air alone is used; this cannot be shown so easily when ventilating with oxygen-enriched mixtures. With such mixtures, hypoventilation and the parallel accumulation of carbon dioxide remain more or less unnoticed. On the other hand, ventilation with air ensures maximum oxygen saturation only when the patient receives a sufficient minute volume; this gives at the same time an assurance that carbon dioxide is being adequately removed.

Near the right end of the oximeter curves (Figs. 6, 7, 8) one can observe small fluctuations in oxygenation when going over from controlled to spontaneous respiration. The mechanism of these fluctuations is not fully understood but they were greater if there was still some respiratory depression due to curare. After giving adequate amounts of Prostigmin and sucking off any secretions, the oximeter curve usually rose to the values obtained initially during spontaneous respiration (Fig. 7). In clinical practice it is not feasible to check these

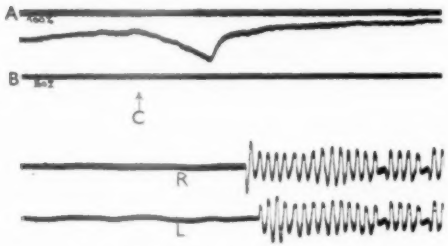

FIG. 4.—A and B are calibration lines for 100% and 50% oxygen saturation. In between the oximeter curve recorded from an ear of the patient. At C intubation was performed with consequent fall in oxygen saturation which lasted only about 30 seconds. The lower two tracings are records from the pneumotachographs.

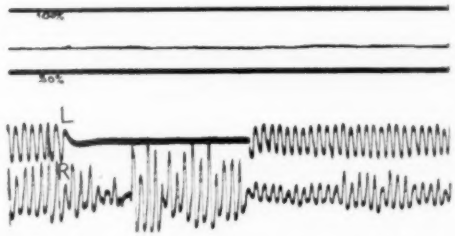

FIG. 5.—Although the left lung was occluded for 1½ minutes, the oximeter tracing remains unaltered. The absolute value of the oximeter tracing is unknown, but only relative changes are of interest for our purposes.

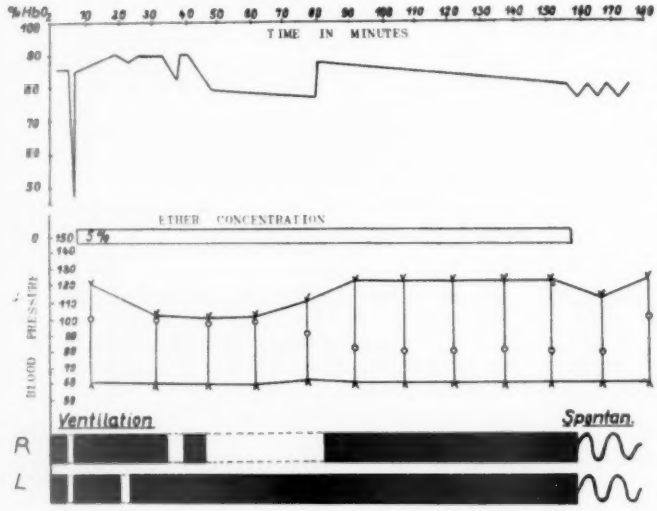

FIG. 6.—After intubation with consequent short-lasting fall in oxygenation, the left and the right branch are alternately occluded, causing only small decreases in oxygenation. During subsequent right upper lobectomy the right branch remains occluded for 30 min. Note relatively small, initial decrease in oxygenation which disappears again soon, although the left lung alone is ventilated with air.

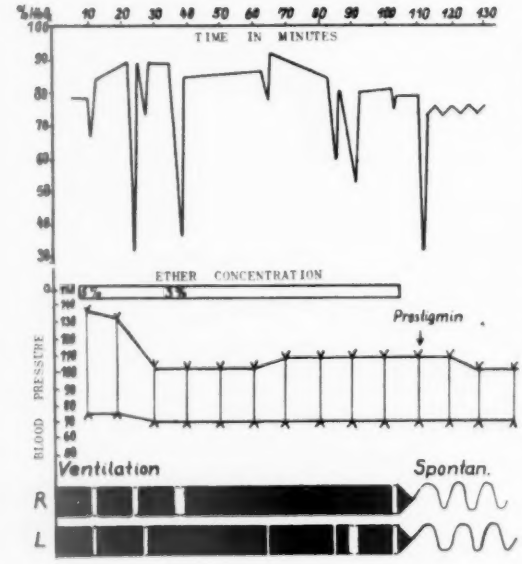

FIG. 7.—The two black bands at the bottom indicate again artificial ventilation of both lungs; white gaps show periods of apnœa caused by clamping one or other branch of the Carlens tube. For over one and a half hours the patient had been receiving 3% ether and curare; although the latter had worn off by the end of the operation, spontaneous respiration was inadequate as shown by the steep fall of the oximeter curve; injection of Prostigmin rapidly brought the oxygenation back to a level close to that at the beginning of the operation.

fluctuations for any length of time It is therefore our contention that it is important to give additional oxygen post-operatively to such patients. When replacing ventilation with air by ventilation with a 4 : 1 nitrous oxide/oxygen mixture either in an open or a closed system, we obtained changes in oxygen saturation similar to that with ventilation with air whenever ventilation was interrupted or one side occluded.

During subsequent operations we ventilated the healthy and the diseased lung separately by means of a Carlens tube. When occluding one lung one may either observe no decrease in oxygenation at all or one may get all degrees of falling off in oxygenation.

The lower tracings in Figs. 4–8 show the ventilation of each lung as well as the intentional interruption of such ventilation. We found that ventilating the healthy lung alone led to practically the same oxygen saturation as that resulting from normal, spontaneous respiration of the same patient (Fig. 5). Ventilation of the diseased lung, however, frequently revealed greater functional impairment than would have been expected from previous X-ray examination. For example, a lung showing only apical tuberculosis on the X-ray picture proved incapable of maintaining full oxygenation (Figs. 6, 7, 8).

Summarizing the findings of our oximetric studies we were able to establish that in certain patients ventilation with air of one lung only is quite adequate to maintain the same blood oxygenation which was obtained when ventilating both sides; on the other hand there are patients with diseased lungs where the separate ventilation of either side always results in a decrease in oxygen saturation.

Carrying out these tests on patients with severely diseased lungs may lead to a rapid decrease of oxygen saturation; we therefore interrupted the experiment whenever the initial

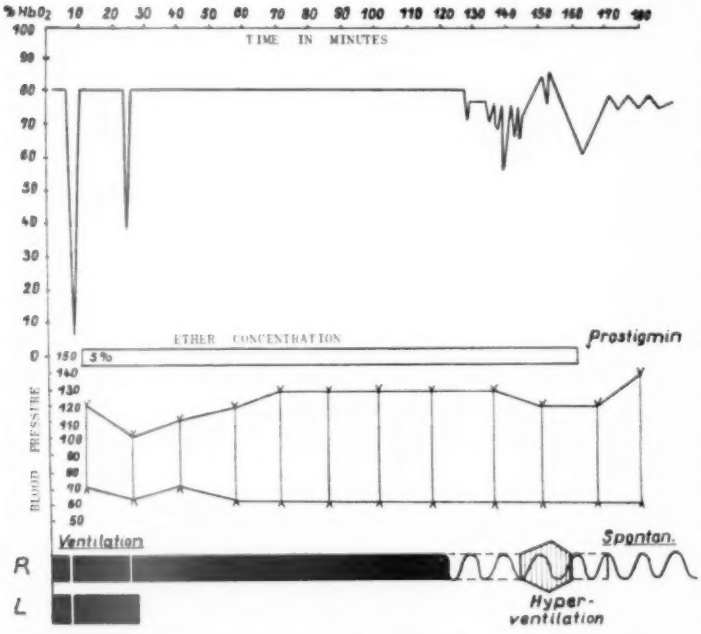

FIG. 8 illustrates how oximetry during breathing of air shows up inadequately assisted ventilation at the conclusion of a left pneumonectomy.

value of saturation had decreased by one-half. The shorter the interval following occlusion of the healthy lung and ventilation of the other side only, during which the oxygenation falls to one-half of the original value, the less satisfactory is the function of the ventilated side.

We also studied this "half-time" on non-anæsthetized patients. It is possible to train a non-intubated patient to hold his breath for a sufficient time to ensure a drop in oxygenation to about one-half of the initial value.

It is also known from incidents during anæsthesia such as intrabronchial hæmorrhage, that profound falls in oxygen saturation can occur without leaving any permanent damage, as long as they last for only a short time. We therefore decided that a brief decrease of oxygen saturation to one-half of the initial value could be permitted without harm in patients with healthy cardiovascular systems. The so-called "half-time" during spontaneous respiration following the closure of one side was used as a measure of the function of the other side of the lung. And we found this of assistance in answering one of the most important questions put by the thoracic surgeon to the anæsthetist and to the lung function expert, namely, will the patient survive a pneumonectomy or, during a partial resection, the temporary loss of function of the whole operated side due to atelectasis?

In order to imitate a situation corresponding to pneumonectomy we have taken two new steps in our lung function tests:

(1) In the patient breathing spontaneously through a double lumen tube, the side to be resected was connected with a to-and-fro system filled with pure nitrogen. In contrast to the method of closing off the lung, this procedure permits unimpeded respiratory movements, and in the conscious patient does not give rise to a feeling of suffocation. If no appreciable fall in oxygen saturation of the blood resulted, the subsequent pneumonectomy was tolerated well by the patient. If there was an appreciable fall in oxygen saturation during such a test, only a partial resection was carried out (Fig. 9).

(2) Anæsthetized patients were given a relaxant and ventilated intermittently with positive-negative pressures via a double lumen tube with pure air; the side of the lung to be resected was either closed off or connected with the to-and-fro system filled with nitrogen. The results were similar to those obtained with the first method.

These experiments do not deal with shunts of the pulmonary circulation which might be of significance after pneumonectomy. However, our results show that any shunts on the non-oxygenated side cannot play such an important part as has been claimed by several authors.

Conclusions.—The results of this investigation were all obtained in operations on the open thorax, often complicated by the loss of large areas of active lung tissue. These extreme conditions permit us to extend our conclusions to operations which interfere much less with the respiratory system. We conclude that expert ventilation with air combined with quantitatively known and easily controllable anæsthetic vapours has a wide range of applications. We have been able to show that one can anæsthetize successfully

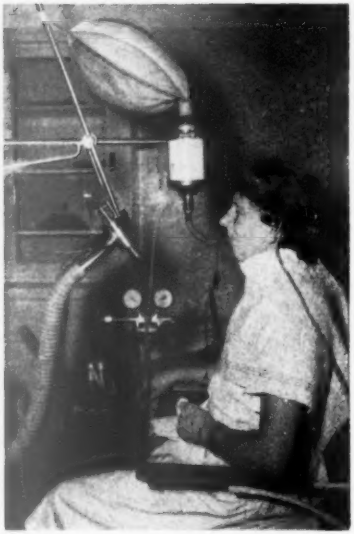

FIG. 9.—Broncho-oximetry immediately prior to broncho-spirometry. Right branch of Carlens tube connected to N_2-filled, to-and-fro system (diseased lung without oxygen supply); left branch (healthy lung) open to air.

and safely without the use of heavy gas cylinders and without soda lime canisters. There are still many parts of the world where such considerations are of vital importance.

The described method of broncho-oximetry is, in our view, a valuable supplement to broncho-spirometry for the assessment of lung function. It may enable a decision to be made between pneumonectomy or partial lung resection.

Professor W. W. Mushin (Cardiff) drew attention to Dr. Poppelbaum's illustrations which showed that when controlled respiration was even momentarily interrupted, the oxygen saturation of the blood fell with startling rapidity to levels at which the patient must have been very cyanosed. He doubted whether this state of affairs was acceptable for patients undergoing thoracic surgery. He asked whether the use of air to ensure elimination of CO_2, by making apparent the need for good ventilation, did not introduce the possibly greater risk of serious oxygen deficiency during the inevitable interruptions in ventilation.

It may be true that some anæsthetists use mixtures of nitrous oxide and oxygen with a proportion of oxygen as in air. Professor Mushin did not support this practice. He considered that an inspired oxygen content of at least 30–50% was necessary for patients on controlled respiration during anæsthesia. In these circumstances interruption of controlled respiration for even a minute or two produced little important change in oxygen saturation of the blood.

Dr. J. Parkhouse (Oxford) said he felt sure Dr. Poppelbaum would be the last person to claim that there was no place for oxygen during anæsthesia. He pointed out that it was quite unfair to compare ether anæsthesia with nitrous oxide anæsthesia on the grounds that there must necessarily be large differences between the two techniques in respect of inspired oxygen concentrations. Although Professor Mushin mentioned using only 50% nitrous oxide, most anæsthetists felt that this was insufficient to maintain unconsciousness, and in the nitrous oxide technique described by Professor Gray (Gray and Riding, 1957, *Anaesthesia*, **12**, 129) it was routine practice to intubate the patient after induction with a gas mixture containing only 20% oxygen. This technique was specifically advocated for poor-risk patients, and was extensively practised without complications. As a recent American publication (Weitzner *et al.*, 1959, *Anesthesiology*, **20**, 624) had reaffirmed, the duration of apnœa was all-important in the development of hypoxia. Furthermore, with nitrous oxide anæsthesia the inspired oxygen concentration was limited, even in emergency situations, by fear of the patient awaking; with Dr. Poppelbaum's technique, on the other hand, it was possible to administer at least 95% oxygen whenever indicated.

In contrast to Professor Mushin's belief, the cumulative experience of the Oxford school over several years had confirmed the impression that the amount of oxygen present in atmospheric air was perfectly adequate for the needs of patients on controlled respiration during general anæsthesia. More recently, a technique similar to Dr. Poppelbaum's had been used for many thoracic and cardiac operations, including extracorporeal circulation and moderate and profound hypothermia: some of these operations required supplementary oxygen but the great majority showed adequate oxygen saturation while being ventilated with room air.

Dr. H. G. Epstein (Oxford) thought that the decrease in oxygenation during intubation was less interesting than the very rapid return to the initial level of oxygenation as soon as ventilation with air had been resumed. Regarding the lowest values of oxygenation, these were probably less excessive than would appear from the graphs; one had to consider that the value of 80% assumed by Dr. Poppelbaum for adequate ventilation with air erred on the low side. Of particular interest seemed to be the finding that breathing of air with one lung alone could maintain the level of oxygenation unaltered.

Dr. Poppelbaum, in reply, recalled that the Section of Anæsthetics had recently discussed the emergency resuscitation and anæsthesia of mass casualties. In such circumstances air should always be considered as a vehicle for anæsthetic vapours since oxygen, nitrous oxide and soda-lime might not be available. He emphasized that in his lecture he had not intended to advocate a sudden and complete change-over to ventilation with air in thoracic surgery in place of the traditional methods; his aim had been to demonstrate the feasibility of the procedure, particularly in uncomplicated cases. Obviously the double bellows unit could be used equally well for nitrous oxide/oxygen mixtures, and a 4 to 1 nitrous oxide/oxygen mixture could justifiable be compared with air since the partial pressures of oxygen were similar. He agreed with Professor Mushin that lower concentrations of nitrous oxide were often used clinically, in which case hyperventilation, whether deliberate or not, helped to maintain anæsthesia.

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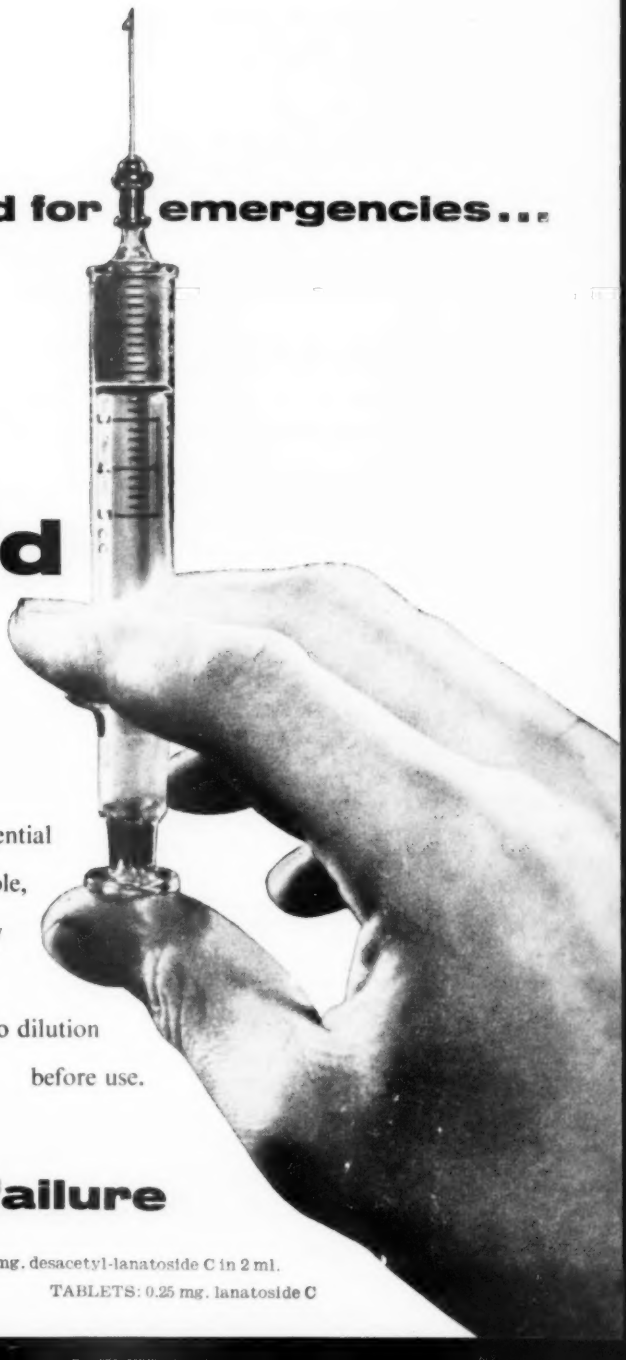

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*REFERENCES

Welsh, A. L., and Ede, M.: J.A.M.A. 166 : 158, 1958

Additional Clinical Publications on Tarcortin: Clyman, S. G.: Postgrad. Med. 21: 309, 1957

Bleiberg, J.: J.M. Soc. New Jersey 53 : 37, 1956

Abrams, B. P., and Shaw, C.: Clin. Med. 3 : 389, 1956

Bleiberg, J.: Am. Practitioner 8 : 1404, 1957

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References: "Clinical Medicine," Vol. 5, No. 4, April, 1958; and "Ohio State Medical Journal," Vol. 55, No. 6, June, 1959.

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Section of Dermatology

President—HUGH GORDON, M.C., F.R.C.P.

Meeting
October 15, 1959

Two Cases of Basal-Cell Congenital Nævus.—PATRICK CLARKSON, F.R.C.S., and HAROLD WILSON, M.D.

Case I.—J. S., male, aged 53. Labourer.

History.—For as long as he can remember he has had multiple painless nodules all over his body. They are most numerous on the face particularly round the eyelids.

Family history.—A sister is similarly affected (Case II). One brother, one sister alive and well. His father was killed in an accident; his mother died, cause unknown, but neither had any skin lesions.

Clinical findings.—Multiple basal-cell lesions are present all over the body, particularly round the eyes. Most of them are nodular but there is a wide variety of lesions. Round the eyes they are ulcerated, on the trunk are several of superficial basal cell pattern. Below the right knee is an indefinite pigmented plaque which is histologically of the same appearance. On the left side is a nephrectomy scar. The second and third toes are webbed on both feet.

Investigations.—Histology: Small rodent ulcers (basal cell carcinomata) in skin of face and back. Lesion from left knee shows small early basal cell carcinoma of skin of multi-focal origin.

X-rays: Teeth and jaw: Upper jaw appears edentulous but several carious and infected stumps are present in the mandibles. There are translucent spaces in the alveoli which appear to be root abscesses rather than cysts. Ribs: There are malformed and bifid ribs on both sides. There is a possibility of incomplete fusion of the neural arches in the cervicodorsal region, and a full series of films of the vertebral column and pelvis is to be done.

The lesion round the eyes has regressed following superficial X-ray therapy.

Comment.—This case is very similar to those described by Howel and Caro (1959) the full clinical features of which are basal-cell nævi at birth or puberty, multiple skin cancers, follicular dental cysts, bifurcation of ribs, milia on the face, epithelial cysts of skin, dorsal scoliosis, agenesis of the corpus callosus, fibroma of ovary, lipoma, feeblemindedness.

REFERENCE

HOWELL, J. B., and CARO, M. R. (1959) *Arch. Derm., Chicago*, **79**, 67.

Case II.—M. S., woman aged 60, sister to Case I. The lesions, small ulcers and red plaques, started to appear diffusely over the trunk, limbs and face twenty years ago. Four years later she had wide areas treated with superficial X-ray. There was steady progress of the lesions in number and in depth of erosion over the next ten years. At this time she was referred to one of us (P. C.). Her particular concern was a cluster of deep ulcers in the right flank (Fig. 1) which was in a clearly dense area of less severe lesions. These ulcers invaded the fat and were painful.

FIG. 1 (*Case II*).—Appearance of right flank just before operation and ten years after onset of ulcers.

Treatment.—A very wide excision was done leaving a defect of about 12 × 15 in. (30 × 38 cm) in the right flank. It was impossible to find any area of her body of this size completely free of basal cell lesions. The grafts which were cut to cover this defect from the left thigh had therefore to be cut through, and hence to contain on themselves, some superficial basal-cell nævi. These grafts took more or less completely. One group of basal cell nævi continued to grow on the grafts

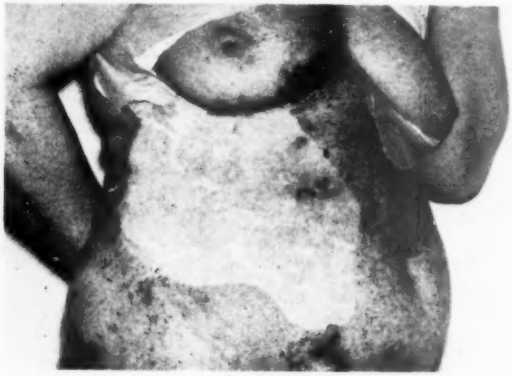

FIG. 2 (*Case II*).—The Thiersch graft cover which contained small areas of nævi from the thigh a year later. Ten years after operation this grafted area is completely free of lesions and the only substantial area of her body to be so.

for a short time (Fig. 2) but after about a year disappeared entirely.

A unique feature, hitherto we believe unrecorded, of this patient is that the extensive grafted area of over 1 sq. ft on her right flank is stable, healed, and remains an island completely free of basal-cell nævi on a trunk which is diffusely and more or less uniformly affected by these lesions.

Dr. Peter Smith: As far as treatment is concerned, is it worth while using Grenz rays? I treated two superficial basal-cell carcinomas with 3,500 r at 10 kV and they have done extremely well; if it does not do any good, it will not do any harm.

Dr. C. D. Calnan: One of the first people to draw attention to cases of multiple nævoid basal-cell epitheliomata was Dr. H. G. Adamson (1908).

I showed two similar cases in 1952 (Calnan, 1953). Apart from Howell's cases, already referred to, similar patients have been presented in San Francisco (Allington, 1959), and in Philadelphia.

Treatment should be undertaken by a team of surgeon, radiotherapist and dermatologist. Many of these lesions can be treated very satisfactorily by diathermy, although the method does require some skill and experience to be effective.

REFERENCES

ADAMSON, H. G. (1908) *Lancet*, ii, 1133.
ALLINGTON, H. V. (1959) *Arch. Derm. Chicago*, **80**, 505.
CALNAN, C. D. (1953) *Brit. J. Derm.*, **65**, 219.

Dr. B. Russell: These patients should be re-examined at frequent intervals, and each lesion treated on its merits by surgery, radiotherapy or cryotherapy. In dealing with this and similar problems it is most valuable to hold combined clinics at which a plastic surgeon and a radiotherapist are present as well as a dermatologist. In consultation the trio can best decide what is the appropriate treatment for the more awkwardly placed lesions.

The President: At the Royal Marsden Hospital we have had under our care two members of a family who are, I think, examples of this condition. The brother started with lesions about the age of 45 and 15 have been treated. His sister is something of a record in that she has had over 150 separate lesions treated, all on the face. We would have liked to treat a great many by diathermy but this was refused by the patient. She illustrates the importance of formication as an early symptom since this is present before any visible signs of a rodent ulcer.

Professor J. T. Ingram: We are familiar with certain nævoid tumours, but this is something quite new to me. I should have thought radiotherapy was undesirable being a carcinogenic agent. I agree with Dr. Calnan as regards team-work in treatment.

Pyoderma Gangrenosum.—D. S. NACHSHEN, M.B. (for I. MUENDE, F.R.C.P.).

Mrs. J. W., aged 31. Driller.

History.—In May 1959, possibly following trauma, there suddenly appeared on the front of the right leg a bulla containing serum, blood, and later pus. The bulla ruptured and the surroundings became red and extended rapidly. During this period, lasting a few days only, coarse granulation tissue appeared in the base of the lesion. The spread was only checked by deep diathermy trenching carried out about 1 in. away from the extending margin. After diathermy the lesion seemed to stop spreading about ½ in. away from the trench and healed rapidly in a few days, leaving a relatively sound scar. Similar progressive lesions subsequently developed on both legs without any previous injury and were treated in the same way. At least one recurrent lesion broke through the line of a previous diathermy trench. The most recent lesion is on the dorsum of the right foot and has not been subjected to diathermy for fear of damaging the extensor tendons. Her general health (apart from anæmia) has been good, and at no time has she had any definite manifestations of colitis.

Investigations.—Cultures from the bullæ were sterile at the time of maximal activity, but the bullæ later became contaminated with *Streptococcus hæmolyticus* and a coagulase-positive *Staph. aureus*. Blood W. R. negative. Hæmoglobin was at one time 57%, increased to 80% by transfusion. W.B.C. 10,500 (polys. 65%, lymphos. 25%, monos. 5%, eosinos. 5%). Serum sodium 140, potassium 5·1, chloride 104 mEq/l. Total plasma proteins 6·6 g%, electrophoresis showing normal gamma-globulin fractions, and a slight increase of the alpha-2 fraction. Urine free of albumin and sugar.

Comment.—Pyoderma gangrenosum was first described by Brunsting *et al.* (1930). Association with ulcerative colitis has been reported by Brunsting (1954) and by Percival (1957), with the hypothesis of synchronous primary epithelial damage to the skin and bowel. In a series of 19 cases, 11 of which had coexistent ulcerative colitis, Perry and Brunsting (1957) found no organism in the skin lesions common to all the cases described. Treatment with sulphapyridine brought improvement in some instances. Marcussen (1955) described a case with accompanying hypogammaglobulinæmia. No biopsy was made in the present case as it was felt that such a procedure might precipitate another spreading lesion. In previously reported examples where biopsies had been taken, histopathological studies did not reveal the possible ætiology, which is so far unknown.

POSTSCRIPT (8.12.59).—She is now having maintenance doses of prednisolone and there have been no recurrences. Her psyche remains unchanged. She has œdema of the right ankle presumably the result of interference with superficial lymphatic drainage by previous diathermy. —D. S. N.

REFERENCES

BRUNSTING, H. A. (1954) *Ohio St. med. J.*, **50**, 1150.
BRUNSTING, L. A., GOECKERMAN, W. H., and O'LEARY, P. A. (1930) *Arch. Derm. Chicago*, **22**, 655.
MARCUSSEN, P. V. (1955) *J. invest. derm.*, **24**, 275.
PERCIVAL, G. A. (1957) *Brit. J. Derm.*, **69**, 130.
PERRY, H. O., and BRUNSTING, L. A. (1957) *Arch. Derm. Chicago*, **75**, 380.

Dr. P. J. Hare: I have treated 3 patients with this disease successfully with steroids in the sense that the ulcers healed. They were alike in other ways. They all had rheumatoid arthritis and they all went crazy when I gave them steroids. However, I do not think that in those instances the lesions were artifacts. I have had a fourth case with an identical clinical picture. She was repeatedly investigated and only after a time did we realize what was going on. On two successive admissions to hospital her serum bromide level was greatly elevated. I have no doubt that she took bromides knowing they would produce the skin lesions—an unusual kind of artifact. She had an unhappy love life and domestic difficulties.

Dr. H. Wilson: I have seen the second case to which Dr. Hare referred, and she has required steroids from time to time, but recently developed a gastric ulcer which perforated and required surgical treatment. At the moment she is having no steroids and her skin is practically normal. I believe that she has been more or less in that condition for several months. I can add another case very similar to the above, but not quite so severe, who was also controlled by steroids. He was an Irish labourer, not very intelligent, but he did not develop mental symptoms when given steroids. I do not consider that either of these cases is an artifact, although I thought at one time that this was the diagnosis in the former case.

Dr. B. Schwartz: I had the privilege of looking after this patient for a time while Dr. Muende was away. I felt, soon after I went into her ward, that because of her general attitude to the condition and the exhibitionist tendencies which she also displayed here this afternoon, this was a case of dermatitis artefacta. Because her original ulcer was attributed to an injury at work she was in receipt of industrial injury benefit and at the time I was looking after her the claim was coming up for reconsideration. The circumstances seemed ideal for the creation of a dermatitis artefacta. The only method I could postulate for the production of new lesions was the injection of some noxious substances under the skin, but we could not find any evidence of this on investigation.

Dr. D. S. Nachshen: I am grateful for the comments, especially in view of the suggestion that this condition might be dermatitis artefacta. We are certain she has an odd psychological make-up and seems to take some kind of strange delight in these lesions, wondering when she is going to have the next diathermy and whether they are ever going to heal up. We have not treated her with steroids at all. We have treated her purely by diathermy, which was thought to be the most rapid method of stopping the most alarming-looking advance of these infected necroses of the skin. At no time have I prescribed bromides or iodides in any form. We have found no evidence of fungal infection either superficial or deep.

The following cases were also shown:

(1) Cutaneous Metastases. (2) Two Cases of Familial Rosacea-like Dermatosis with Lanugo Hair Changes.—Dr. H. WILSON.

Lupus Vulgaris Treated with Diethyl Dithioliso-phthalate.—Dr. C. W. MARSDEN.

Eczema Vaccinatum.—Dr. J. MORGAN.

Multiple Basal Cell Epitheliomata.—Dr. O. L. S. SCOTT and Dr. D. BETT.

Case for Diagnosis. ? Polyarteritis Nodosa.—Dr. E. N. M. JOHNSTON.

Meeting
November 19, 1959

Pemphigus Vegetans Complicated by Peripheral Vascular Disease. — MAURICE GARRETTS, M.R.C.P. (for P. J. HARE, M.R.C.P.).

J. W. H., male, aged 69. Retired.

History.—This man developed an oozing blistered plaque in his left inguinal region in February 1952. After treatment in hospital with cortisone, an average daily dose of 100 mg was maintained for two years. He was maintained on cortisone 75 mg daily (or its equivalent in prednisone or prednisolone) until May 1959, when it was possible to reduce this to prednisolone 5 mg b.d. On this he has remained well, with the help of hydrocortisone ointment applied locally.

He complained of rheumatism in both legs and has had a typical history of intermittent claudication for the past twelve months.

Clinical findings.—Pigmented plaque in left inguinal region with occasional tiny blisters.

Investigations.—On examination by a vascular surgeon evidence of bilateral femoral artery blockage was discovered. The patient declined operation (arterial grafting).

Pemphigus Foliaceus Complicated by Peripheral Vascular Disease. — MAURICE GARRETTS, M.R.C.P. (for P. J. HARE, M.R.C.P.).

A. H., male, aged 58. Carpenter and joiner.

History.—In May 1957, the patient developed a boil on his sternum, and soon afterwards a blistering disease spread over most of his body surface. He was treated with prednisolone 100 mg daily, gradually reduced to 5 mg b.d., and the disease was brought under control.

Six months ago, he suddenly awoke one morning with a pain in his right calf. The right foot became swollen for a few days. Since then he has had intermittent claudication, the pain in the right calf bringing him to a halt after 100 yards.

Clinical findings.—Warty lesions with occasional flaccid blisters dotted over most of the back and chest, the remains of his pemphigus foliaceus.

Investigations.—Two months ago the right popliteal fossa was explored. A narrowing blocked popliteal artery was revealed, and it was considered unsuitable for arterial graft operation. The gastrocnemius muscle was denervated.

Discussion.—Both these cases have developed arterial thrombosis while being treated with steroids for pemphigus. Ziprkowski *et al.* (1959) reported 2 cases of arterial thrombosis apparently due to steroid treatment. In one the thrombosis affected the brachial artery while in the other the superficial femoral artery was thrombosed. Both cases were treated with steroids for pemphigus. Grossgriff *et al.* (1950) described 11 cases of thrombo-embolic phenomena in a series of 175 cases receiving cortisone for various diseases. Changes were found which indicated a hypercoagulable state of the blood. In the cases reported by Ziprkowski *et al.* no such changes were demonstrable.

We wish to stress that the cases described by Ziprkowski *et al.*, and our cases all suffered from pemphigus. The association between a rare disorder such as pemphigus with a relatively common one, arterial thrombosis, is difficult to evaluate. While there is not enough evidence to conclude that either pemphigus or steroid treatment is ætiologically related to the development of peripheral vascular disease, the cases reported by Ziprkowski together with our own two cases make it prudent to look out for similar sequelæ in the future.

REFERENCES

GROSSGRIFF, S. W., DIEFENBACH, A. F., and VOGT, W. (1950) *Amer. J. Med.*, **9**, 752.

ZIPRKOWSKI, L., SCHEWACH-MILLET, M., and MOZES, M. (1959) *Brit. J. Derm.*, **71**, 223.

Dr. J. Morgan: I had a case five or six years ago, a man aged 65, with severe pemphigus foliaceus. He had steroids, but in those days I was not prepared to give the patient a very big dose. I feel sure we did not give him enough; he died within a few months. He did, however, develop on the dose—the equivalent of about 200 mg of cortisone daily over a period of about three months—a blockage of the brachial artery.

Hereditary Hæmorrhagic Telangiectasia.—V. R. BLOOM, B.M. (for E. J. MOYNAHAN, F.R.C.P.).

C. P., female, aged $4\frac{1}{2}$.

History.—Red mark noticed on face at 1 year. This has gradually increased in size and has bled once. A smaller red mark was noticed on the back of the right hand one year ago.

There are numerous small red marks on the faces of paternal grandmother, father and two siblings, the last three having suffered from epistaxis. One other sibling had epistaxis and has early lesions of the nasal mucosa.

Clinical findings.—Area of variable erythema measuring $\frac{1}{2} \times 2\frac{1}{2}$ in. below the right zygoma. Pressure at five discrete points produces disappearance of the erythema. There is a typical stellate hæmangioma on the dorsum of the right hand.

There is no evidence of mucous membrane involvement.

Investigations.—Chest X-ray normal; Hb 12·6 g%; M.C.H.C. 32%; W.B.C. 10,600, normal differential; platelets appear normal; bleeding time (Duke) 6 minutes; clotting time (Dale and Laidlaw) 2 min 10 sec.

(*Meeting to be continued*)

BOOK REVIEWS

Clinical Gastroenterology. By Eddy D. Palmer, M.D., F.A.C.P. (Pp. vii+630; illustrated. £6 17s. 6d.) London: Cassell. 1957.

This comprehensive account of disease of the gastro-intestinal tract is a useful book of reference for the specialist who wants to keep abreast of the modern American point of view; it is clearly illustrated but some of the X-ray reproductions could be improved upon in a subsequent edition. To the British reader it does seem unfortunate that there is no reference to British teachings. Thus there is no mention of aspirin as a cause of erosions of the stomach; it will come as a surprise to many that chronic gastritis does not occur as a result of chronic alcoholism: and that an uncomplicated duodenal ulcer requires little special attention and that dietary treatment has no virtue. While agreeing with the author that emotional strains play an important part in producing gastro-intestinal diseases, it seems to us that this aspect is unduly stressed throughout the volume. With these reservations this book can be recommended as a clearly set out and comprehensive exposition of a group of disorders which are widespread at the present time.

The Story of the Peptic Ulcer. By Richard D. Tonkin, M.D., F.R.C.P. Characterized by Raymond Keith Hellier, F.R.S.A. (Pp. 71; illustrated. 16s.) Philadelphia and London: Saunders. 1957.

Peptic ulcer as a stress disease is discussed in this short essay, amusingly illustrated by drawings and caricatures of those who suffer from this disorder, and showing how they should deal with their symptoms and treatment. Good advice is tendered as to diet, medicinal treatment and the mental attitudes to be adopted in treatment. This very unusual presentation from an authoritative source will have a popular appeal to the victims of this disorder—especially so in the U.S.A. where this pictorial approach will be particularly useful to the lay public.

Oxygen Supply to the Human Fœtus. A Symposium organized jointly by the Council for International Organizations of Medical Sciences and the Josiah Macy Jr. Foundation. Edited by James Walker and Alec C. Turnbull. (Pp. xii+313; illustrated. 47s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This is a verbatim record of a symposium on "The Oxygen Supply to the Human Fœtus" which took place in Princeton in December 1957. A distinguished international panel of speakers took part, representing obstetrics and gynæcology, pædiatrics, physiology, embryology and other allied sciences. The main topics were physiology of oxygen transport, anatomy, utero-placental blood flow and oxygen consumption, cord blood oxygen levels, techniques and asphyxia and fœtal distress. This volume thus represents perhaps the most complete study of the problem of oxygen supply to the fœtus ever undertaken.

The editors are to be congratulated on the way in which they have made a mass of incohesive data into an eminently readable and informative volume. The reports on the discussions of each paper make particularly good reading. It is to be regretted that a clear summary of each paper was not given. Many obstetricians and pædiatricians may find the detailed physiological data difficult; nevertheless this comprehensive exploration of territory, surprisingly little explored before, has resulted in a new and original approach to an all-important subject.

Readings on Race. Edited by Stanley M. Garn, Ph.D. (Pp. viii+281. 54s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960.

This book consists of reprints of 17 articles published in the British and American literature between 1952 and 1958. They are introduced by Dr. Garn, who has selected them to show how radically in the last ten years the impact of modern genetical theory upon physical anthropology has changed the approach of physical anthropologists to questions of race. There are two papers under the heading "A contemporary definition of race", one by Garn himself on "Race and Evolution"; there is one paper by Hulse concerning past and present population size amongst human races; one on disease selection and race, dealing with the anthropological implications of sickle-cell gene distribution in West Africa; and a paper by Allison on aspects of polymorphism in man. Genetic drift is considered in two papers, one the 1952 paper of Bentley Glass and his colleagues on genetic drift in religious isolates. Racial intermixture is dealt with by A. F. Roberts and by Glass. The largest single section is devoted to climate and race, though the fundamental initial papers on this subject by E. Schreider are inexplicably omitted. There are lastly two papers on experimental studies of racial differences, both concerning the effect of exposure to cold. It is easy to criticize the selection of papers since no two editors would agree entirely, but Dr. Garn has provided an excellent book of very readable proportions. The book can

heartily be recommended to all those who wish to learn something of how modern human biologists think of this war-torn subject.

Variations on a Theme by Sydenham: Smallpox. By P. B. Wilkinson, M.R.C.P. (Pp. 40+36 plates. 17s. 6d.) Bristol: John Wright & Sons Ltd. 1959.

This monograph gives the clinical features of an epidemic of smallpox which attacked Hong Kong in 1937–8. It began early in the winter of 1937 and reached its peak in March 1938. 860 patients were admitted to the smallpox hospital, of whom 810 had smallpox. The author's careful bedside study of the manifestations of the disease is of value as are the numerous photographs illustrating the lesions. The case-mortality appears to have been high, although details are not given. Convalescent serum intramuscularly or intravenously appeared to be the only treatment worth pursuing. Historical tribute is paid to Sydenham who differentiated smallpox from measles and scarlet fever. The book is admirably produced.

The Biological, Sociological and Psychological Aspects of Aging. By Kurt Wolff, M.D. (Pp. 95. 27s. 6d.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

Dr. Wolff has made a timely and a useful contribution to the study of aspects of ageing in a form which is interesting to doctors and can easily be read by the lay public. He writes simply but obviously from a wealth of clinical experience and much of what he writes is of profound importance. In his introduction, Dr. Wolff draws attention to the increased life expectancy at birth and, while pointing out that in addition to a biological aspect ageing has also a sociological and a psychological side, he wisely emphasizes the need for more psychiatric treatment and rehabilitation for geriatric patients.

The biological section is interesting and contains some practical advice on diet as well as referring to the influences of heredity and the reactions to stress and tension. In the section on the sociological aspect Dr. Wolff discusses retirement, the cultural attitude of society to elderly people and the feeling of economic insecurity. These are all important problems and are much in the minds of the more intelligent members of the public as well as the concern of the medical profession, social workers and others. The psychological aspect touches on the most difficult aspect of ageing and one about which least is known. This section, although the most complex, is perhaps the most interesting and should be useful to those who seek knowledge in this field. The ample references introduce a wider field to all who wish to study the subject.

Peripheral Facial Palsy: Pathology and Surgery. By Karsten Kettel, M.D. (Pp. 341; illustrated. £6.) Oxford: Blackwell Scientific Publications. 1959.

This monograph gives a very full and detailed description of the facial nerve and its disorders. The subject is examined from all aspects and the bibliography is very complete. The author has made a special study of this subject and has written many authoritative papers since 1942. On reading this book it is clear that it is written by an author who has been giving continuous thought to this relatively small subject over many years.

The paper and lay-out are good and the book is very lavishly illustrated, the illustrations being very well reproduced. There is no index, but the list of contents is so comprehensive that it is easy to find what is wanted without the help of an index.

There is no doubt that this book gives the most complete picture of facial nerve disorders seen from an otological point of view available, at this moment, in the English language. It can be confidently recommended to practising otologists and to all candidates for examinations where this subject may be considered at a high level.

Medical Radiographic Technic. Edited by Glenn W. Files, revised by W. L. Bloom, Jr., *et al.* 2nd edit. (Pp. 386; illustrated. 82s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

This well-known book on radiographic technique, originally edited by Glenn W. Files, has been reprinted eleven times, which is a tribute to its popularity; it has now been revised and re-edited.

In the section on apparatus construction all the basic principles and modern developments of tube construction and high output generators have been well covered. There is a very adequate and well-written section on basic radiographic technique supplemented by good anatomic diagrams and well-chosen photographs demonstrating the various radiographic positions. Together with these photographs are published standard radiographs and basic exposure tables.

The section on special procedures is not entirely satisfactory; it is much too short and inadequately documented. In just over 20 pages the authors have tried to cover all specialized radiographic methods, including such examinations as angiocardiography, cerebral angiography, pyelography and pelvimetry.

These omissions should not, however, detract from the value of the book, which is a good short text of basic radiographic technique and should retain its past popularity. The production of the volume is of a high standard; great credit goes to the publishers for their efforts.

Practical Allergy. By M. Coleman Harris, M.D., F.A.C.P., and Norman Shure, M.D., M.S., F.A.C.P. (Pp. xiii + 471; illustrated. 52s. 6d.) Philadelphia: F. A. Davis Company. 1957.

This book is written for doctors who do not specialize in allergy but nevertheless deal with patients suffering from allergic disorders. A great deal of information is provided in a compact form about the diagnosis and treatment of these conditions. It is written clearly and the definitions of such terms as "allergy", "hypersensitivity" and "asthma" are brief and accurate. The chapters dealing with history taking and drug reactions are excellent, and there is useful information concerning the distribution of common inhalant allergens in household materials and common causes of contact allergy. Practical instructions are given for the preparation of extracts and the care of equipment.

One is nevertheless left with the impression that the authors have attempted to cover too wide a field, so that much of the information is very superficial. This is particularly true of the chapter on collagen diseases. Certain features of considerable importance are dealt with in a sketchy and almost offhand manner—these include respiratory function tests, inhalation tests for allergens, mould sensitivity in asthma and steroid therapy. For a book which is intended to be a practical aid the approach is too vague. Clear indications for treatment, and precise information relating to the method of administration and dosage of drugs are seldom given: thus, referring to ACTH, "The initial dose should be large enough to induce a favourable response . . . ." (p. 336). The inclusion of a section on materia medica does not entirely compensate for these shortcomings

The index is adequate and a bibliography is appended.

Cancer of the Breast. Compiled and edited by Willard H. Parsons, M.D., F.A.C.S. American Lecture Series No. 355. (Pp. xv + 232; illustrated. 60s.) Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1959.

In a disease so common as cancer of the breast, which accounts for 25% of all malignant diseases in women, a new book is always welcome. This book consists of ten chapters written by twelve experts, either individually or in co-operation.

In Chapter II Dr. Foote calls attention to the large proportion of tumours excised as "innocent" and found to have some malignant cells, and the large number of patients suffering from cancer who have had a previous history of treatment for a benign condition.

The chapter on diagnosis is for the family doctor perhaps the most important of all. The importance of self-examination of the breasts by the patient is rightly stressed. Some people may doubt whether more than simple palpation should be taught, as other signs such as asymmetry of the two breasts, the level of the nipples &c., may be mistaken and lead to much unnecessary worry. In England there is still some prejudice against self-examination or indeed of any cancer education, but this is gradually being overcome.

Chapter IV deals with pre- and post-operative care, both of great importance. The suggestion, however, that in the case of coronary occlusion there must be a postponement of the mastectomy for *six months* suggests that it would be simpler to order the coffin. The authors are right in considering the psychologic management of the patient before and after operation to be of paramount importance.

The chapter on hormone therapy is very interesting, and there is no doubt that hormone and chemotherapy are becoming more and more important.

Although it is not quite clear for which section of the profession the book is intended, it is clearly written and well illustrated and must be of interest to every general practitioner.

Osteochondritis Dissecans. Loose Bodies in Joints. Etiology, Pathology, Treatment. By I. S. Smillie, O.B.E., Ch.B., F.R.C.S.(Ed.), F.R.F.P.S. (Pp. viii + 224; illustrated. 60s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

This excellent monograph is based on a study of 300 cases and the author postulates four lesions, similar radiologically but different pathologically: anomalies of ossification, juvenile osteochondritis dissecans, adult osteochondritis dissecans and tangential osteochondral fractures. The hypothesis is that all four are related in the ætiology of osteochondritis dissecans. Factors considered to play important parts in the production of this lesion are local vascular deficiency, trauma and endocrine or constitutional abnormalities. In the juvenile the lesion is produced by trauma in ischæmic bone, but in the adult trauma leads to ischæmia and then osteochondral fracture. Individual joints in which the lesion is described in some detail are the knee, the metatarsophalangeal (Freiberg's infraction),

elbow, ankle and hip; in the hip the relationship between osteochondritis dissecans and Perthe's disease is discussed, ischæmia forming the basic pathology.

In the knee the author finds no evidence in his series of true spontaneous healing, and it may well be that in the past confusion has arisen from the disappearance of anomalies of ossification.

There is no doubt that this book provides a great deal of food for thought and discussion. It makes excellent reading and is beautifully illustrated. The author presents a logical argument for his suggestions of "conservative surgery", but the book must be read in the spirit of seeking after truth rather than factual dogma.

Medical Aspects of Amateur Boxing. Issued by the London Amateur Boxing Association. (Pp. 63. 2s. 6d.) London: Amateur Boxing Association. 1959.

This is an odd publication, made up of a series of papers, some of which seem to have been *ad hoc* written contributions, and others to have been spoken addresses. One paper seems to comprise merely a collection of notes or headings. Another chapter bears little or no reference to the topic of boxing. The section which deals with eye injuries makes grim reading, especially in a pamphlet which purports to defend the practice of amateur boxing. Perhaps this little book represents the very last word in favour of a very shaky cause.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P. 6th ed. (Pp. xii+751; illustrated. 45s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

This book is now more than half as big again as when it first appeared twelve years ago. It must be admitted that not all its content comes under the heading of medical emergencies—broken hypodermic needles, for instance, and wax in the ear, and electrical wiring hardly qualify, though it is easy to understand how they come to be put in—but it is quite evident that no resident staff quarters in any hospital should be without a copy close at hand. The chapters on renal disease and on industrial medicine are outstanding. The final 120 pages are devoted to practical procedures, and include a full and admirably illustrated discussion on artificial respiration, and the addresses and telephone numbers of centres specialising in the unusual, e.g. snake-bite, toxoplasmosis, poliomyelitis, hæmophilia, and so on. The index is good.

It is a little disappointing not to be given the source of quotations; thus, on page 216, "Sudden spontaneous happenings within the cranium are vascular in origin", and again, of contusion, on page 221, "the mechanism of the body is intact, but the government has departed". These are striking aphorisms which would tempt a practitioner to read more of that author if his name were known. On the other hand, "a case of blighted ovum", page 107, is a very ugly phrase, and that diagnosis is not listed in the latest edition of the "Nomenclature of Disease". These are but minor blemishes in a remarkable production, which may be confidently recommended to all who practise medicine.

Your Health and Your Wealth. By a doctor. (Pp. vi+139. 7s. 6d.) Bristol: John Wright & Sons Ltd. 1959.

This book purports to be a plea for restraint in the use of the National Health Service. There are a large number of examples of abuse and ignorance on the part of patients, the mania for hospital treatment, and the performance of unnecessary tests and operations. These are illustrated by lurid examples, some of which are of great antiquity. "Most of the general practitioners after a few years are heading for a nervous breakdown, if not a physical and mental breakdown."

As to remedies, patients who attend hospital too frequently should attend "Talk Centres" at which they could discuss their fears and troubles with a psychologist, a physician and the family doctor. Old people should be cared for by welfare groups headed by a local personage of repute and sympathy whose services should be rewarded by Citizenship of the Town or Freedom of the City.

For no apparent reason a chapter on the administration of the N.H.S. is inserted. Sir James Stirling Ross is called "Doctor James Sterling Ross".

An account of the biological history of man is followed by general advice on health. Some of this is sensible enough, but readers will be surprised to learn that a man who has a row with his wife should "take the dog out for a walk or even get drunk (this is not to be repeated though)". Sitting or standing leaning forward for long periods will cause the stomach to hang forwards, forming a pool in which the acid juice collects, which eventually erodes the gastric lining. Obesity can be cured by a kind of Couéism—"Every day I get slimmer and slimmer". Pavlov's work on dogs was awful torture and suffering. The well-known fact that a fox, while being hunted, will stop to catch a hen is adduced to prove that foxes suffer from gastric ulcer.

And so on and so on. Altogether a dreadful book.

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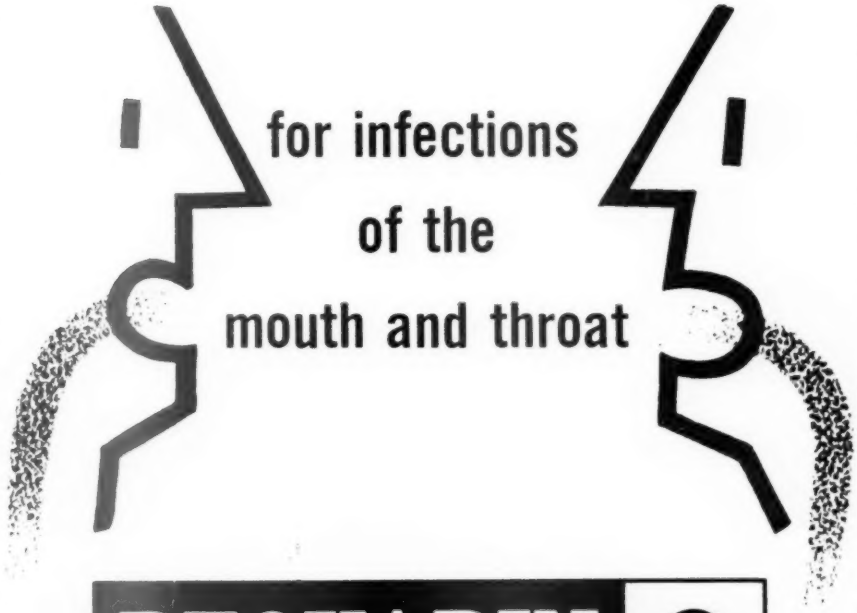

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